Cardiovascular Health Summit Advances in Interventional Cardiology 2007

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Cribier-Edwards percutaneous valve

Watchman Left Atrial Exclusion Device

Webb, J. G. et al. Circulation 2006;113:842-850

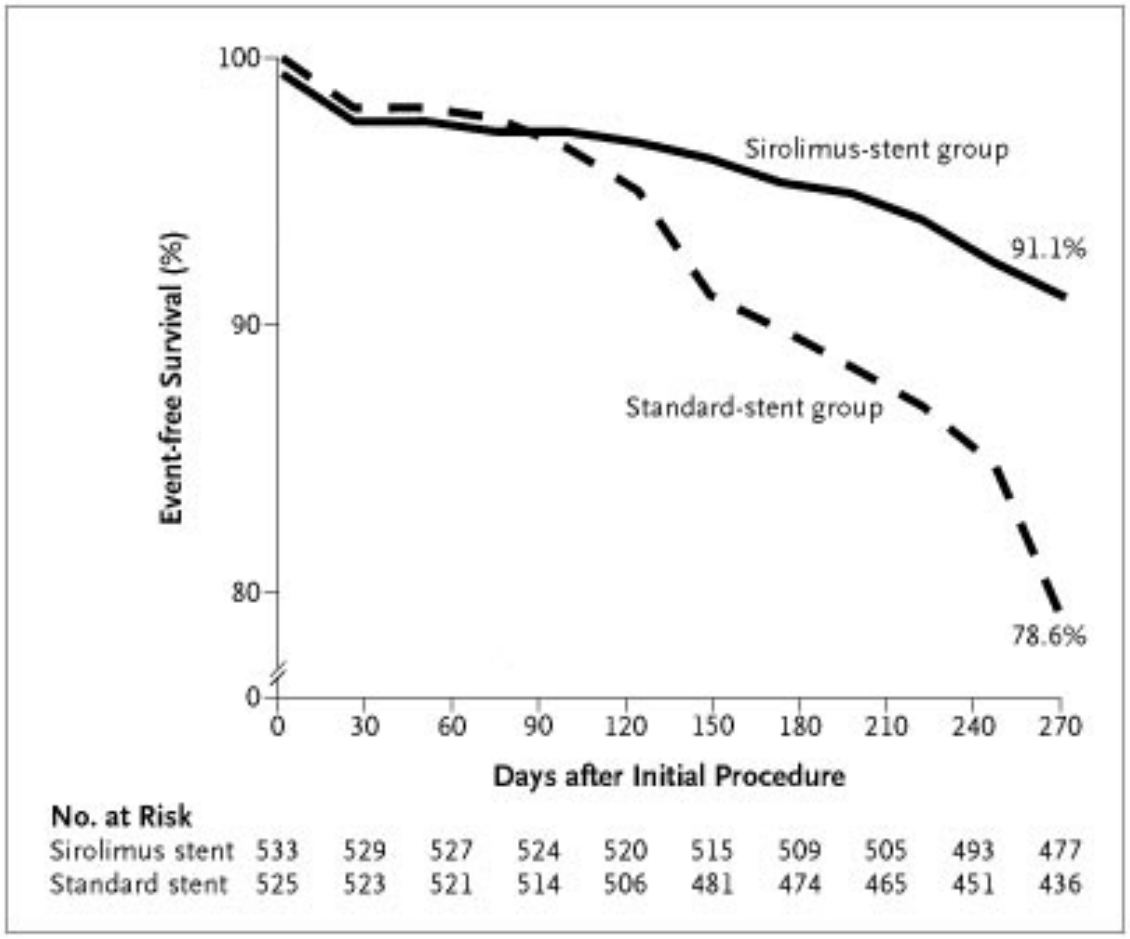
Drug-Eluting Stent Thrombosis

- Andreas Gruentzig: PTCA 1977
- 15 years of acute closure and restenosis
- Stents (bare metal stainless steel): Benestent and Stress Trials: mid 90s
- New problems:
  - Stent thrombosis: -optimal deployment
    -dual antiplatelet therapy
  - In stent restenosis: Drug-Eluting Stents (DES) available in the early 2000s: The Holy Grail

Drug-Eluting Stent Thrombosis

- Drug-Eluting Stent (DES) early 2000s:
  - Stainless steel stents
  - Active Drug (sirolimus or paclitaxel)
  - Drug embedded in a non-bioerodable polymer
- Sirolimus-eluting stent (SES): Cypher
  Cordis, Johnson and Johnson
- Paclitaxel-eluting stent (PES): TAXUS
  Boston Scientific
- Denovo lesions, native coronary arteries, stable or unstable angina, lesion lengths 28-30mm

Sirolimus: SIRIUS Investigators
Survival Free from Target-Vessel Failure
SES vs BMS



Moses J et al. N Engl J Med 2003;349:1315-1323

Sirolimus: SIRIUS Investigators: 9 month Outcome for SES vs BMS

Table 3. Major Adverse Cardiac Events in the Hospital and outside of the Hospital during 270 Days of Follow-up.*

Variable	Sirolimus-Stent Group (N=533)	Standard-Stent Group (N=525)	P Value
	no. of patients (%)		
In-hospital events			
Death	1 (0.2)	0	
Myocardial infarction	12 (2.3)	8 (1.5)	
Q-wave	2 (0.4)	0	
Non–Q-wave	10 (1.9)	8 (1.5)	
Target-lesion revascularization	1 (0.2)	0	
CABG	0	0	
PTCA	1 (0.2)	0	
Any major adverse cardiac event	13 (2.4)	8 (1.5)	
Out-of-hospital events			
Death	4 (0.8)	3 (0.6)	
Myocardial infarction	3 (0.6)	9 (1.7)	
Q-wave	2 (0.4)	2 (0.4)	
Non–Q-wave	1 (0.2)	7 (1.3)	0.04
Target-lesion revascularization	21 (3.9)	87 (16.6)	<0.001
CABG	3 (0.6)	8 (1.5)	
PTCA	19 (3.6)	83 (15.8)	<0.001
Any major adverse cardiac event	26 (4.9)	93 (17.7)	<0.001
Cumulative to 270 days			
Death	5 (0.9)	3 (0.6)	
Myocardial infarction	15 (2.8)	17 (3.2)	
Q-wave	4 (0.8)	2 (0.4)	
Non–Q-wave	11 (2.1)	15 (2.9)	
Target-lesion revascularization	22 (4.1)	87 (16.6)	<0.001
CABG	3 (0.6)	8 (1.5)	
PTCA	20 (3.8)	83 (15.8)	<0.001
Any major adverse cardiac event	38 (7.1)	99 (18.9)	<0.001
Target-vessel failure	46 (8.6)	110 (21.0)	<0.001
Stent thrombosis	2 (0.4)	4 (0.8)	

Primary Endpoint

Moses J et al. N Engl J Med 2003;349:1315-1323

Paclitaxel: TAXUS IV
Clinical Outcomes at Nine Months

Table 3. Clinical Outcomes at Nine Months.

Outcome	Paclitaxel-Eluting Stent (N=662)	Bare-Metal Stent (N=652)	Relative Risk (95% CI)*	P Value
	percent			
Death from cardiac causes	1.4	1.1	1.27 (0.47–3.38)	0.80
Myocardial infarction	3.5	3.7	0.94 (0.54–1.66)	0.88
Q-wave	0.8	0.3	2.46 (0.48–12.60)	0.45
Non–Q-wave	2.7	3.4	0.81 (0.44–1.49)	0.52
Stent thrombosis	0.6	0.8	0.79 (0.21–2.92)	0.75
In hospital	0	0.3	—	0.25
Up to 1 mo after discharge	0.3	0.3	0.98 (0.14–6.97)	1.00
>1–6 mo	0.3	0.2	1.97 (0.68–5.73)	1.00
>6–9 mo	0	0	—	—
Target-lesion revascularization	3.0	11.3	0.27 (0.16–0.43)	<0.001
Percutaneous coronary intervention	2.4	8.7	0.28 (0.16–0.48)	<0.001
Coronary-artery bypass grafting	0.6	3.1	0.20 (0.07–0.57)	<0.001
Target-vessel revascularization†	4.7	12.0	0.39 (0.26–0.59)	<0.001
Percutaneous coronary intervention	3.6	9.0	0.40 (0.25–0.64)	<0.001
Coronary-artery bypass grafting	1.1	3.4	0.31 (0.13–0.33)	0.005
Within 1 mo	0	0.3	—	0.25
>1–9 mo	4.7	11.7	0.40 (0.27–0.60)	<0.001
Major adverse cardiac events‡	8.5	15.0	0.56 (0.41–0.77)	<0.001
Within 1 mo	2.9	2.5	1.17 (0.61–2.25)	0.73
>1–9 mo	5.7	12.7	0.45 (0.31–0.65)	<0.001
Target-vessel failure§	7.6	14.4	0.52 (0.38–0.73)	<0.001
Within 1 mo	2.6	2.5	1.05 (0.53–2.05)	1.00
>1–9 mo	5.1	12.1	0.42 (0.29–0.62)	<0.001

* CI denotes confidence interval.
† Patients undergoing both percutaneous coronary intervention and coronary-artery bypass grafting during follow-up are counted as having a single target-vessel revascularization event.
‡ Major adverse cardiac events were death from cardiac causes, myocardial infarction, or ischemia-driven target-vessel revascularization.
§ Target-vessel failure was defined by death, myocardial infarction, or ischemia-driven revascularization related to the target vessel.

Primary Endpoint

Stone G et al. N Engl J Med 2004;350:221-231

Drug-Eluting Stent

- Reduction of instent restenosis rates by 75% into the single digits at 9 and 12 months
- FDA approval with increasing off label use
- Dual antiplatelet therapy with Aspirin and Clopidogrel for at least 3 months for SES and at least 6 months for PES (instructions for use)
- “New medicines and new methods of cure always work miracles…..for a while” (William Heberden, MD) from Keriakes et al JAMA 2007;297:209-211

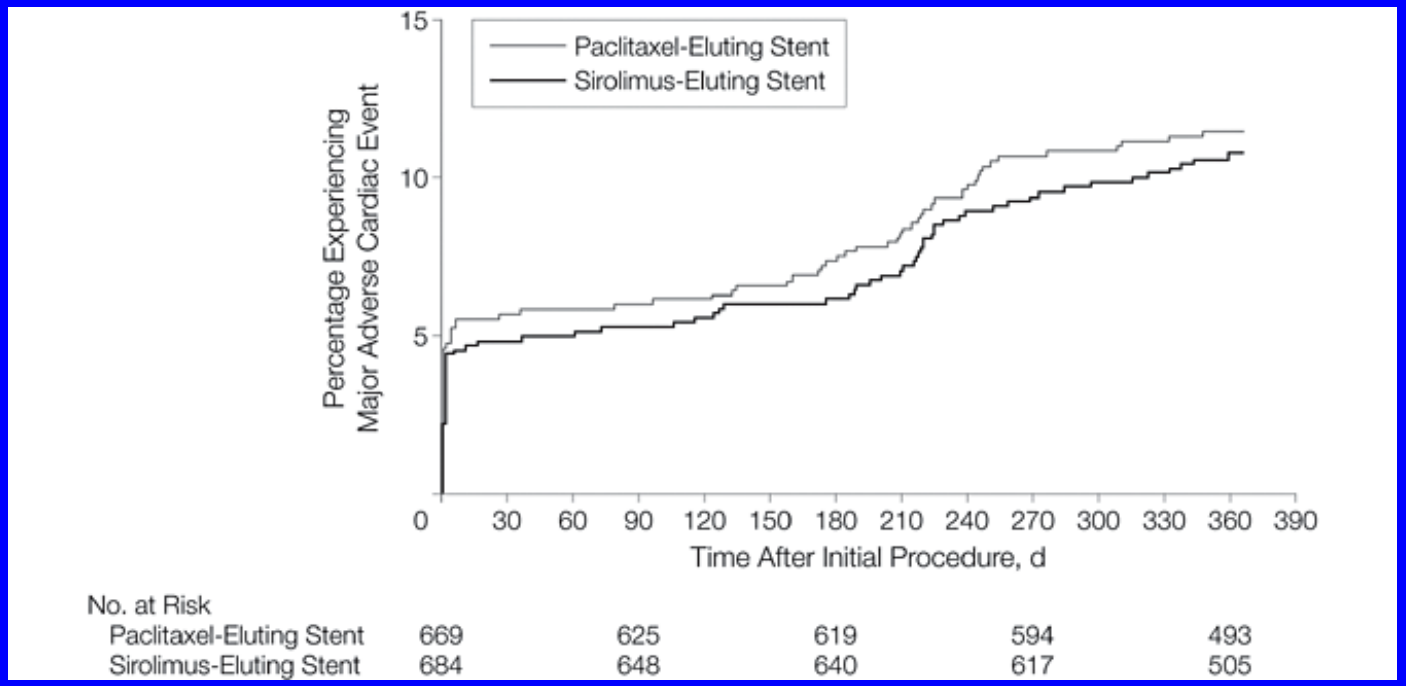
Head-to-Head Comparison of SES vs PES: 1,386 patients

Table 5. Major Adverse Clinical Events During 12 Months of Follow-up*

	No. (%) of Patients			
	Sirolimus-Eluting Stent (n = 684)	Paclitaxel-Eluting Stent (n = 669)	Relative Risk (95% Confidence Interval)	*P* Value
Major adverse cardiac events†				
Death	16 (2.3)	9 (1.3)	1.74 (0.77-3.91)	.23
Cardiac	10 (1.5)	7 (1.0)	1.40 (0.54-3.65)	.63
Noncardiac	6 (0.9)	2 (0.3)	2.93 (0.59-14.49)	.29
Myocardial infarction	35 (5.1)	40 (6.0)	0.86 (0.55-1.33)	.55
Q-wave	1 (0.1)	8 (1.2)	0.12 (0.02-0.97)	.02
Non–Q-wave	34 (5.0)	32 (4.8)	1.04 (0.65-1.66)	.90
Target lesion revascularization	41 (6.0)	41 (6.1)	0.98 (0.64-1.49)	>.99
Surgical	4 (0.6)	6 (0.9)	0.65 (0.18-2.30)	.54
Percutaneous	37 (5.4)	38 (5.7)	0.95 (0.61-1.48)	.91
Overall	73 (10.7)	76 (11.4)	0.94 (0.69-1.27)	.73
Other adverse clinical events				
Target vessel revascularization‡	14 (2.0)	12 (1.8)	1.14 (0.53-2.45)	.84
Surgical	4 (0.6)	2 (0.3)	1.96 (0.36-10.64)	.69
Percutaneous	10 (1.5)	10 (1.5)	0.98 (0.41-2.33)	>.99
Target vessel failure	82 (12.0)	86 (12.9)	0.93 (0.70-1.24)	.68
Stent thrombosis	5 (0.7)	13 (1.9)	0.37 (0.13-0.49)	.06
Acute	2 (0.3)	4 (0.6)	0.49 (0.09-2.66)	.45
Subacute	3 (0.4)	7 (1.0)	0.42 (0.11-1.61)	.22
Late	0	2 (0.3)	. . .	.15
Cerebrovascular accident	4 (0.6)	6 (0.9)	0.65 (0.18-2.30)	.54
Hemorrhage	35 (5.1)	39 (5.8)	0.88 (0.56-1.37)	.63
Major	9 (1.3)	14 (2.1)	0.63 (0.27-1.44)	.30
Minor	27 (3.9)	26 (3.9)	1.02 (0.60-1.72)	>.99
Major vascular complications	15 (2.2)	20 (3.0)	0.73 (0.38-1.42)	.39

Morice, M.-C. et al. JAMA 2006;295:895-904.

12-Month Incidence of Major Adverse Cardiac Events



11.4%
10.7%

Morice, M.-C. et al. JAMA 2006;295:895-904.

So what happened?

Maisel W. N Engl J Med 2007;356:981-984

Drug-Eluting Stent Thrombosis

- 2003-2004: Occasional case reports of late stent thrombosis after DES began to emerge
- First big bang: March 2006 ACC Atlanta
- Presentation of the BASKET-LATE Investigators
- 988 CONSECUTIVE (non-selected) patients randomized 2:1 DES:BMS
- 746 patients alive without MACE 6 months after coronary stenting; CLOPIDOGREL stopped:
  - BMS Vision stent, Guidant Corp: 281
  - SES: 264
  - PES: 281
- Clopidogrel stopped at 6 months and then followed for another 12 months

Pfisterer et al J Am Coll Cardiol 2006;48:2584-91

BASKET-LATE: Late Catch up

- **Overall** (0-18 month) rates of death and MI were the same: BMS 7.5% vs DES 8.4% p=0.63
- **First 6 months** Death and MI: BMS 12.1% vs DES 7.2% p=0.02
- **AFTER DISCONTINUATION of CLOPIDOGREL (months 7-18)**
  - Death: BMS 0% vs DES 1.2%
  - MI: BMS 1.3% vs DES 4.1%
  - Death and MI: BMS 1.3% vs DES 4.9% (p=0.03)
  - All 6 deaths in the DES group
  - 20/23 MI in the DES group
- Hypothesis generating, to say the least

Pfisterer et al J Am Coll Cardiol 2006;48:2584-91

Meta analyses presented: ESC

- European Society of Cardiology meeting Barcelona September 2006

  Death/Q wave MI 2.6% TAXUS vs 2.3% BMS (p=0.66)

  Death/Q wave MI 6.3% Cypher vs 3.9% BMS (p=0.03)

  Camenzind and Nordmann et al

- Industry data: Cordis/Johnson and Johnson and Boston Scientific
- FDA: Initial Statement on Coronary Drug Eluting Stents, September 14th 2006
- FDA: Special Expert Advisory Committee, December 7th and 8th 2006
- New England Journal of Medicine: March 8th 2007

Clinical Outcomes at 4 Years

Table 3. Clinical Outcomes at 4 Years, According to Kaplan–Meier Estimates.*

Outcome	Sirolimus-Eluting Stent (N=878)	Bare-Metal Stent (N=870)	Hazard Ratio (95% CI)†	P Value‡	Paclitaxel-Eluting Stent (N=1755)	Bare-Metal Stent (N=1758)	Hazard Ratio (95% CI)†	P Value‡
	no. (%)				*no. (%)*			
Stent thrombosis								
Patients with any event	10 (1.2)	5 (0.6)	2.00 (0.68–5.85)	0.20	20 (1.3)§	14 (0.9)	1.44 (0.73–2.84)	0.30
0 to 30 days after procedure	4 (0.5)	1 (0.1)	3.98 (0.45–35.62)	0.23	8 (0.5)	10 (0.6)	0.80 (0.32–2.03)	0.79
>30 days to 4 yr after procedure	6 (0.7)	4 (0.5)	1.50 (0.42–5.30)	0.57	12 (0.8)	4 (0.3)	3.03 (0.98–9.38)	0.04
>30 days to 1 yr after procedure	1 (0.1)	4 (0.5)	0.25 (0.03–2.22)	0.18	4 (0.2)	2 (0.1)	2.01 (0.37–10.97)	0.28
>1 to 4 yr after procedure	5 (0.6)	0	NA	0.025	9 (0.7)	2 (0.2)	4.54 (0.98–21.03)	0.028
Death								
From all causes	57 (6.7)	45 (5.3)	1.27 (0.86–1.88)	0.23	86 (6.1)	92 (6.6)	0.94 (0.70–1.26)	0.68
0 to 30 days after procedure	1 (0.1)	1 (0.1)	0.99 (0.06–15.86)	1.00	2 (0.1)	5 (0.3)	0.40 (0.08–2.07)	0.43
>30 days to 4 yr after procedure	56 (6.6)	44 (5.2)	1.27 (0.86–1.89)	0.23	84 (6.0)	87 (6.3)	0.97 (0.72–1.31)	0.85
>30 days to 1 yr after procedure	10 (1.1)	6 (0.7)	1.66 (0.60–4.56)	0.32	26 (1.5)	26 (1.5)	1.00 (0.58–1.73)	0.99
>1 to 4 yr after procedure	46 (5.5)	38 (4.6)	1.21 (0.79–1.87)	0.37	58 (4.6)	61 (4.9)	0.96 (0.67–1.37)	0.81
From cardiac causes	29 (3.5)	23 (2.7)	1.26 (0.73–2.18)	0.40	36 (2.4)	42 (3.0)	0.86 (0.55–1.35)	0.51
From noncardiac causes	28 (3.3)	22 (2.7)	1.27 (0.73–2.23)	0.40	50 (3.8)	50 (3.7)	1.01 (0.68–1.49)	0.98
Myocardial infarction								
Patients with any event	55 (6.4)	53 (6.2)	1.03 (0.71–1.51)	0.86	111 (7.0)	105 (6.3)	1.06 (0.81–1.39)	0.66
0 to 30 days after procedure	22 (2.5)	17 (2.0)	1.29 (0.68–2.42)	0.43	66 (3.8)	55 (3.1)	1.20 (0.84–1.72)	0.31
>30 days to 4 yr after procedure	34 (4.1)	37 (4.4)	0.91 (0.57–1.45)	0.69	49 (3.6)	54 (3.5)	0.91 (0.62–1.34)	0.62
>30 days to 1 yr after procedure	11 (1.3)	19 (2.2)	0.57 (0.27–1.20)	0.13	14 (0.8)	31 (1.8)	0.45 (0.24–0.85)	0.01
>1 to 4 yr after procedure	23 (2.8)	18 (2.2)	1.28 (0.69–2.37)	0.43	36 (2.8)	25 (1.8)	1.45 (0.87–2.42)	0.15
Q-wave	18 (2.1)	11 (1.3)	1.64 (0.77–3.47)	0.19	22 (1.4)	17 (1.1)	1.30 (0.69–2.45)	0.42
Non–Q-wave	38 (4.5)	43 (5.0)	0.88 (0.57–1.36)	0.55	91 (5.8)	90 (5.3)	1.02 (0.76–1.36)	0.92
Death or myocardial infarction	100 (11.6)	89 (10.4)	1.12 (0.84–1.49)	0.44	187 (12.4)	183 (11.8)	1.03 (0.84–1.26)	0.79
Death or Q-wave myocardial infarction	70 (8.2)	54 (6.4)	1.30 (0.91–1.86)	0.14	105 (7.3)	107 (7.5)	0.99 (0.76–1.29)	0.93
Myocardial infarction or death from cardiac causes	75 (8.8)	70 (8.2)	1.07 (0.77–1.48)	0.69	139 (8.9)	136 (8.5)	1.03 (0.81– 1.30)	0.82
Revascularization								
Target lesion	66 (7.8)	202 (23.6)	0.29 (0.22–0.39)	<0.001	166 (10.1)	338 (20.0)	0.46 (0.38–0.55)	<0.001
Target vessel	102 (12.1)	235 (27.5)	0.38 (0.30–0.48)	<0.001	272 (17.2)	409 (24.7)	0.62 (0.53– 0.73)	<0.001

* Percentages are cumulative Kaplan–Meier estimates, taking into account data from patients who were lost to follow-up at different times, and may thus differ from simple binary percentages. Only the first event was counted within any interval. CI denotes confidence interval.
† The estimate was calculated from a Cox proportional-hazards model.
‡ P values were calculated by a two-sided log-rank test or exact log-rank test.
§ One patient had two episodes of stent thrombosis, one before 1 year and one after 1 year.

Stone G et al. N Engl J Med 2007;356:998-1008

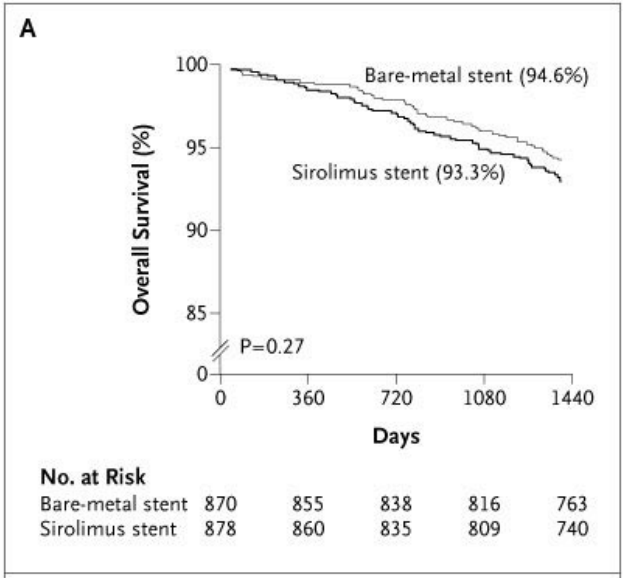
Pooled Analysis of Trials of the Sirolimus-Eluting Stent: Outcomes over 4 years

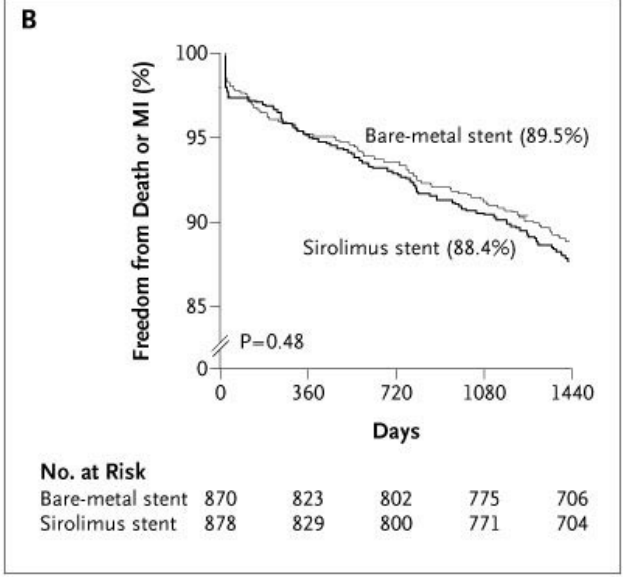
- RAVEL
- SIRIUS
- E-SIRIUS
- C-SIRIUS
- Patient level data for a total of 1748 patients

Clinical Outcome
SES (n=878) vs BMS (n=870)

Death

Death/MI





5.4%

6.7%

p=0.28

10.5%

11.6%

p=0.48

Spaulding C et al. N Engl J Med 2007;356:989-997

DES vs BMS

- First Point:
  - No mortality difference
  - No MI difference
- Second Point: At least that can be demonstrated with the numbers studied and the duration of follow up

Next Point: Stent Thrombosis First, what's the definition? Study Protocol

- Timing:
  - Acute: within 24 hours
  - Subacute: Day 1-30
  - Late: after more than 30 days

Definition of Stent Thrombosis: Study Protocol

- Definition:
  - Acute and Subacute:
    - Vessel occlusion on angiography
    - Recurrent MI in the territory of the stented vessel
    - Death from cardiac causes
  - Late:
    - Recurrent MI with vessel occlusion on angiography
- Secondary thrombosis is excluded

Protocol Stent Thrombosis: Definition and Timing

- If a patient develops restenosis of the target lesion, undergoes reintervention and SUBSEQUENTLY has a stent thrombosis, then it ain’t counted……..
- Reason: To try to focus on the risk of the original stent procedure

Stent Thrombosis: Alternative Definition

- Definitions developed during Summer 2006 by a consortium of academic investigators, regulators and industry representatives
- The Academic Research Consortium (ARC)
- ARC Definitions

Stent Thrombosis: ARC Definition

- Definite:
  - angiographic thrombus, with or without vessel occlusion
  - associated with clinical, EKG or enzymatic evidence of acute ischemia or infarction
- Probable:
  - unexplained death within 30 days of the index procedure
  - MI *at any time* in the territory of the stented vessel *in the absence of angiographic confirmation of stent thrombosis*
- Possible:
  - unexplained death occurring more than 30 days after the index stent

Stent Thrombosis: ARC Definition and Timing

- **Secondary Thrombosis is included**
- Timing:
  - Acute: within 24 hours
  - Subacute: Day 1-30
  - Late: 31 days to 1 year
  - Very late: after 1 year

Incidence of Stent Thrombosis over1440 Days

Table 2. Incidences of Death, Myocardial Infarction, and Stent Thrombosis after 1440 Days of Follow-up.*

End Point	Sirolimus-Stent Group (N=878)	Bare-Metal–Stent Group (N=870)	Adjusted Hazard Ratio (95% CI)	P Value
	number (percent)			
Death	57 (6.7)	46 (5.4)	1.24 (0.84–1.83)	0.28
Cardiovascular cause	29 (3.5)	23 (2.7)	1.26 (0.73–2.18)	0.40
Noncardiovascular cause	28 (3.3)	23 (2.8)	1.22 (0.70–2.11)	0.49
MI	55 (6.4)	53 (6.2)	1.03 (0.71–1.51)	0.86
Q-wave	18 (2.1)	11 (1.3)	1.64 (0.78–3.47)	0.20
Non–Q-wave	37 (4.3)	43 (5.0)	0.85 (0.55–1.33)	0.48
Death or Q-wave MI	70 (8.2)	55 (6.5)	1.28 (0.90–1.82)	0.17
Death or any MI	100 (11.6)	90 (10.5)	1.11 (0.83–1.47)	0.48
Stent thrombosis as defined in protocols†				
Acute	0	0	—	
Subacute	4 (0.5)	1 (0.1)	4.02 (0.45–35.98)	0.21
Late	6 (0.7)	4 (0.5)	1.50 (0.42–5.30)	0.53
Stent thrombosis as defined by the ARC‡				
Acute	0	0	—	
Subacute	4 (0.5)	3 (0.5)	1.34 (0.30–5.93)	0.70
Late	3 (0.3)	11 (1.3)	0.18 (0.04–0.81)	0.03
Very late	23 (2.8)	14 (1.7)	1.65 (0.85–3.20)	0.14
Definite	10 (1.2)	7 (0.8)	1.43 (0.54–3.76)	0.47
Definite or probable	13 (1.5)	15 (1.8)	0.87 (0.41–1.82)	0.70
Any	30 (3.6)	28 (3.3)	1.07 (0.64–1.79)	0.80

* All percentages are based on Kaplan–Meier estimates. Numbers of patients for death or Q-wave myocardial infarction (MI) and death or any MI do not total the sums for each end point alone because some patients had both end points. CI denotes confidence interval.

† Definitions of stent thrombosis according to the study protocols were as follows: acute, within 24 hours after the procedure; subacute, within 1 to 30 days after; and late, more than 30 days after.

‡ Definitions of stent thrombosis according to the Academic Research Consortium (ARC) were as follows: acute, within 24 hours after the procedure; subacute, within 1 to 30 days after; late, between 31 days and 1 year after; and very late, more than 1 year after. See text for details on stent-thrombosis adjudication per protocol and per ARC definitions.

10 vs 5

13 vs 15

Spaulding C et al. N Engl J Med 2007;356:989-997

Pooled Analysis of Trials of Sirolimus- and Paclitaxel- Eluting Stents: Outcomes over 4 years

- TAXUS-I, TAXUS-II, TAXUS-IV, TAXUS-V and TAXUS VI
  - 3513 patients
- RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS
  - 1748 patients

Clinical Outcomes at 4 Years

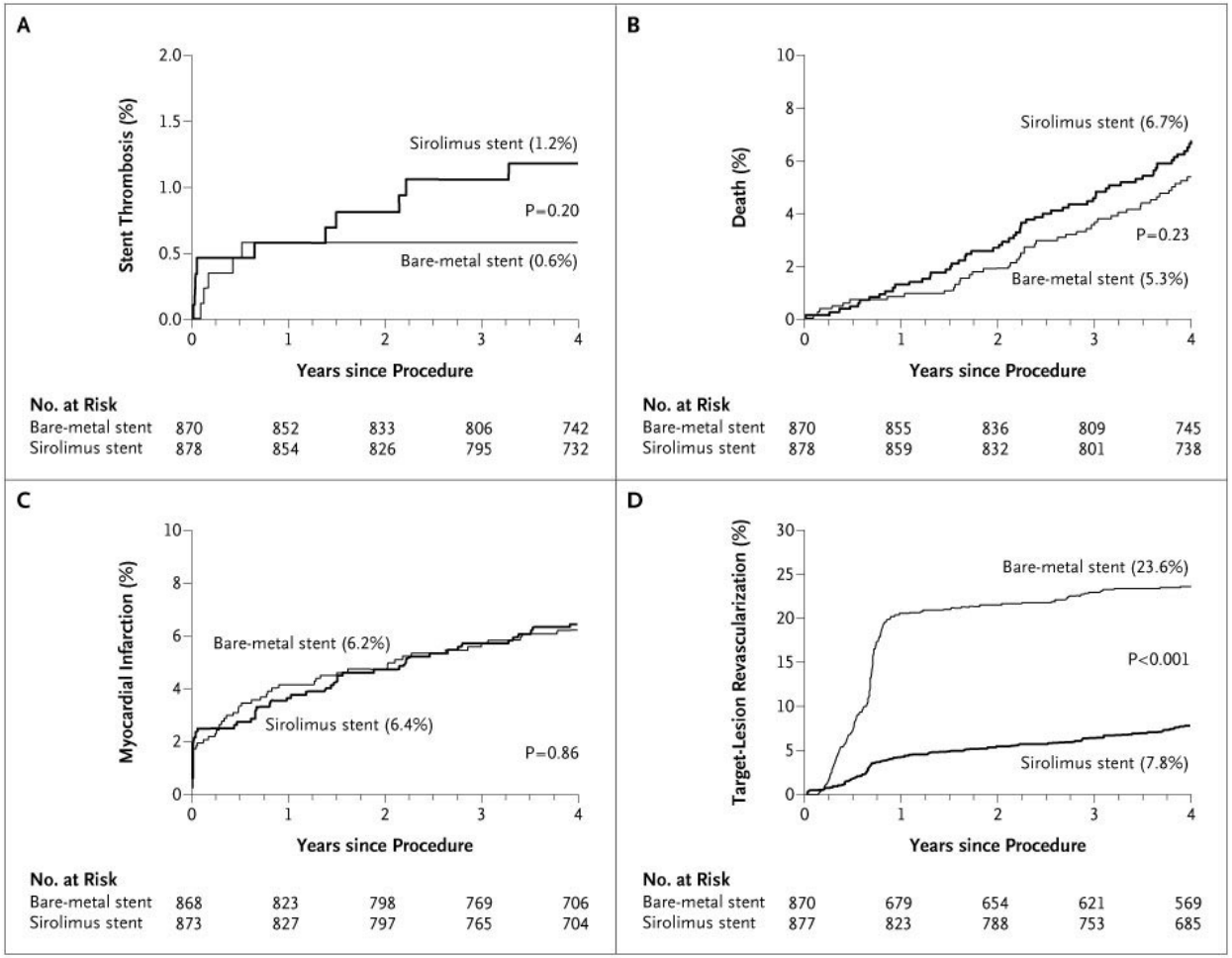
Table 3. Clinical Outcomes at 4 Years, According to Kaplan–Meier Estimates.*

Outcome	Sirolimus-Eluting Stent (N=878)	Bare-Metal Stent (N=870)	Hazard Ratio (95% CI)†	P Value‡	Paclitaxel-Eluting Stent (N=1755)	Bare-Metal Stent (N=1758)	Hazard Ratio (95% CI)†	P Value‡
	no. (%)				*no. (%)*			
Stent thrombosis								
Patients with any event	10 (1.2)	5 (0.6)	2.00 (0.68–5.85)	0.20	20 (1.3)§	14 (0.9)	1.44 (0.73–2.84)	0.30
0 to 30 days after procedure	4 (0.5)	1 (0.1)	3.98 (0.45–35.62)	0.23	8 (0.5)	10 (0.6)	0.80 (0.32–2.03)	0.79
>30 days to 4 yr after procedure	6 (0.7)	4 (0.5)	1.50 (0.42–5.30)	0.57	12 (0.8)	4 (0.3)	3.03 (0.98–9.38)	0.04
>30 days to 1 yr after procedure	1 (0.1)	4 (0.5)	0.25 (0.03–2.22)	0.18	4 (0.2)	2 (0.1)	2.01 (0.37–10.97)	0.28
>1 to 4 yr after procedure	5 (0.6)	0	NA	0.025	9 (0.7)	2 (0.2)	4.54 (0.98–21.03)	0.028
Death								
From all causes	57 (6.7)	45 (5.3)	1.27 (0.86–1.88)	0.23	86 (6.1)	92 (6.6)	0.94 (0.70–1.26)	0.68
0 to 30 days after procedure	1 (0.1)	1 (0.1)	0.99 (0.06–15.86)	1.00	2 (0.1)	5 (0.3)	0.40 (0.08–2.07)	0.43
>30 days to 4 yr after procedure	56 (6.6)	44 (5.2)	1.27 (0.86–1.89)	0.23	84 (6.0)	87 (6.3)	0.97 (0.72–1.31)	0.85
>30 days to 1 yr after procedure	10 (1.1)	6 (0.7)	1.66 (0.60–4.56)	0.32	26 (1.5)	26 (1.5)	1.00 (0.58–1.73)	0.99
>1 to 4 yr after procedure	46 (5.5)	38 (4.6)	1.21 (0.79–1.87)	0.37	58 (4.6)	61 (4.9)	0.96 (0.67–1.37)	0.81
From cardiac causes	29 (3.5)	23 (2.7)	1.26 (0.73–2.18)	0.40	36 (2.4)	42 (3.0)	0.86 (0.55–1.35)	0.51
From noncardiac causes	28 (3.3)	22 (2.7)	1.27 (0.73–2.23)	0.40	50 (3.8)	50 (3.7)	1.01 (0.68–1.49)	0.98
Myocardial infarction								
Patients with any event	55 (6.4)	53 (6.2)	1.03 (0.71–1.51)	0.86	111 (7.0)	105 (6.3)	1.06 (0.81–1.39)	0.66
0 to 30 days after procedure	22 (2.5)	17 (2.0)	1.29 (0.68–2.42)	0.43	66 (3.8)	55 (3.1)	1.20 (0.84–1.72)	0.31
>30 days to 4 yr after procedure	34 (4.1)	37 (4.4)	0.91 (0.57–1.45)	0.69	49 (3.6)	54 (3.5)	0.91 (0.62–1.34)	0.62
>30 days to 1 yr after procedure	11 (1.3)	19 (2.2)	0.57 (0.27–1.20)	0.13	14 (0.8)	31 (1.8)	0.45 (0.24–0.85)	0.01
>1 to 4 yr after procedure	23 (2.8)	18 (2.2)	1.28 (0.69–2.37)	0.43	36 (2.8)	25 (1.8)	1.45 (0.87–2.42)	0.15
Q-wave	18 (2.1)	11 (1.3)	1.64 (0.77–3.47)	0.19	22 (1.4)	17 (1.1)	1.30 (0.69–2.45)	0.42
Non–Q-wave	38 (4.5)	43 (5.0)	0.88 (0.57–1.36)	0.55	91 (5.8)	90 (5.3)	1.02 (0.76–1.36)	0.92
Death or myocardial infarction	100 (11.6)	89 (10.4)	1.12 (0.84–1.49)	0.44	187 (12.4)	183 (11.8)	1.03 (0.84–1.26)	0.79
Death or Q-wave myocardial infarction	70 (8.2)	54 (6.4)	1.30 (0.91–1.86)	0.14	105 (7.3)	107 (7.5)	0.99 (0.76–1.29)	0.93
Myocardial infarction or death from cardiac causes	75 (8.8)	70 (8.2)	1.07 (0.77–1.48)	0.69	139 (8.9)	136 (8.5)	1.03 (0.81– 1.30)	0.82
Revascularization								
Target lesion	66 (7.8)	202 (23.6)	0.29 (0.22–0.39)	<0.001	166 (10.1)	338 (20.0)	0.46 (0.38–0.55)	<0.001
Target vessel	102 (12.1)	235 (27.5)	0.38 (0.30–0.48)	<0.001	272 (17.2)	409 (24.7)	0.62 (0.53– 0.73)	<0.001

* Percentages are cumulative Kaplan–Meier estimates, taking into account data from patients who were lost to follow-up at different times, and may thus differ from simple binary percentages. Only the first event was counted within any interval. CI denotes confidence interval.
† The estimate was calculated from a Cox proportional-hazards model.
‡ P values were calculated by a two-sided log-rank test or exact log-rank test.
§ One patient had two episodes of stent thrombosis, one before 1 year and one after 1 year.

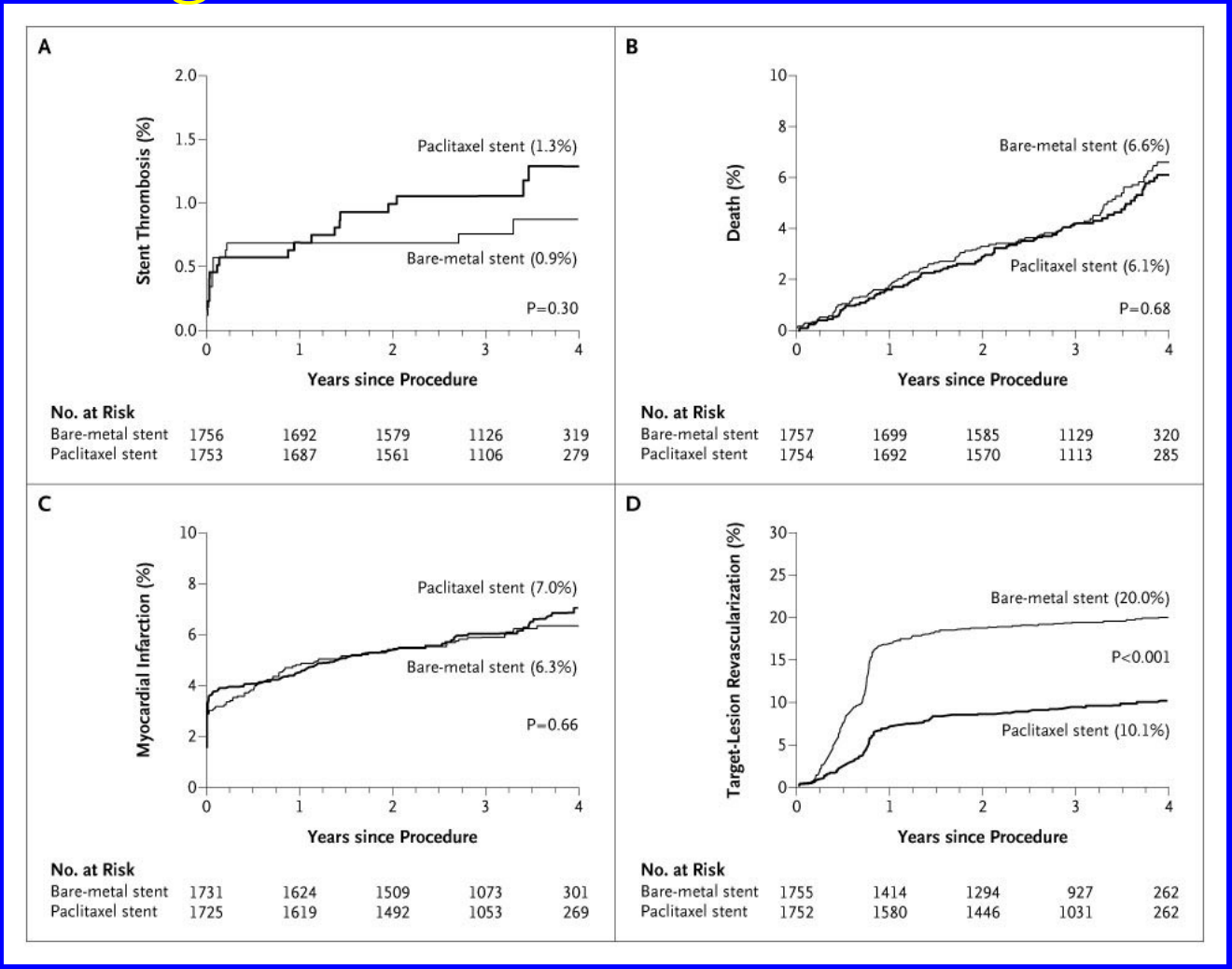
Stone G et al. N Engl J Med 2007;356:998-1008

SES vs BMS over 4 years: Stent Thrombosis, Death, MI, and Target-Lesion Revascularization



Stone G et al. N Engl J Med 2007;356:998-1008

PES vs BMS over 4 years: Stent Thrombosis, Death, MI, and Target-Lesion Revascularization



Stone G et al. N Engl J Med 2007;356:998-1008

Protocol and ARC Definitions of Stent Thrombosis in SES and PES: Total and VLST

	SES	BMS		PES	BMS
Overall					
Protocol	10 (1.2%)	5 (0.6%)		16 (1.3%)	10 (0.8%)
ARC definite or probable	13 (1.5%)	15 (1.7%)		22 (1.8%)	18 (1.4%)
Very Late Stent Thrombosis (>365 days)					
Protocol	5 (0.6%)	0		6 (0.6%)	1 (0.2%)
ARC definite or probable	8 (0.9%)	4 (0.4%)		10 (0.9%)	7 (0.6%)

Mauri L et al. N Engl J Med 2007;356:1020-1029

Clinical Outcomes in Patients after Definite or Probable Stent Thrombosis

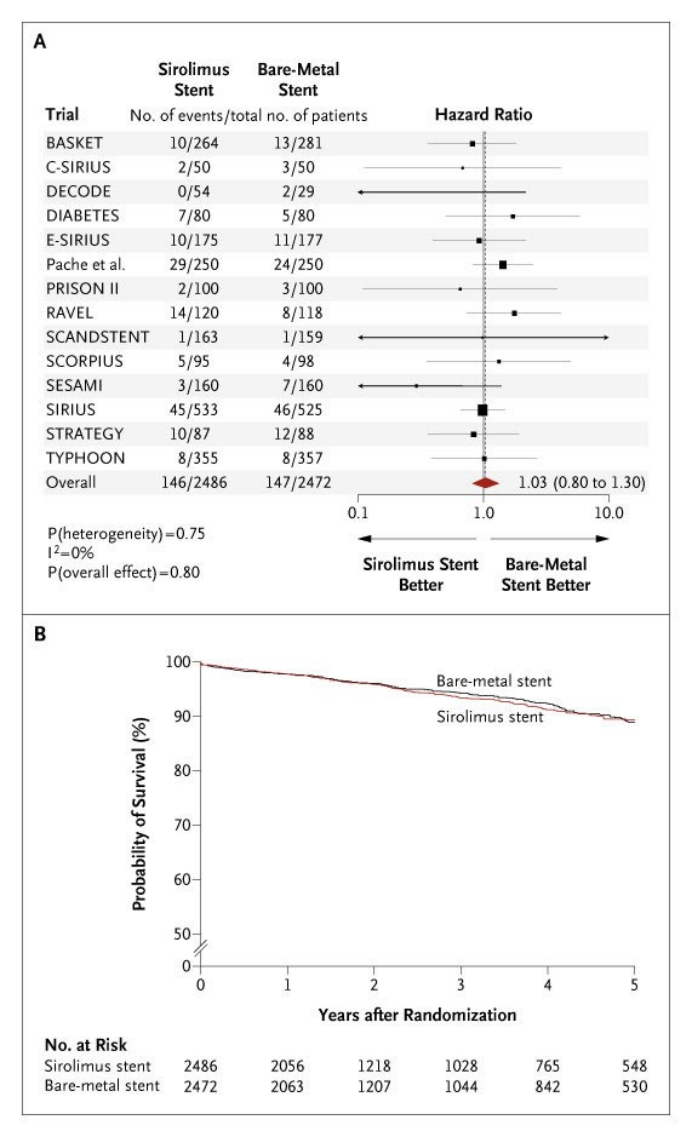
Table 3. Clinical Outcomes in Patients after Definite or Probable Stent Thrombosis.*

Variable	Sirolimus-Stent Trials		Paclitaxel-Stent Trials	
	Sirolimus Stent (N=13)	Bare-Metal Stent (N=15)	Paclitaxel Stent (N=22)	Bare-Metal Stent (N=18)
	no. of events (%)			
Death	4 (30.8)	5 (33.3)	7 (31.8)	5 (27.8)
Myocardial infarction				
Any event	13 (100)	13 (86.7)	17 (77.3)	14 (77.8)
Fatal event	4 (30.8)	4 (26.7)	4 (18.2)	3 (16.7)
Q-wave	8 (61.5)	5 (33.3)	7 (31.8)	5 (27.8)
Non–Q-wave	5 (38.5)	9 (60.0)	10 (45.5)	10 (55.6)

* The definition of definite or probable stent thrombosis is based on criteria set by the Academic Research Consortium (ARC). One patient with a bare-metal stent had both Q-wave and non–Q-wave myocardial infarctions at different times.

Mauri L et al. N Engl J Med 2007;356:1020-1029

The Last Analysis: 14 Trials of SES vs BMS 5-Year Survival

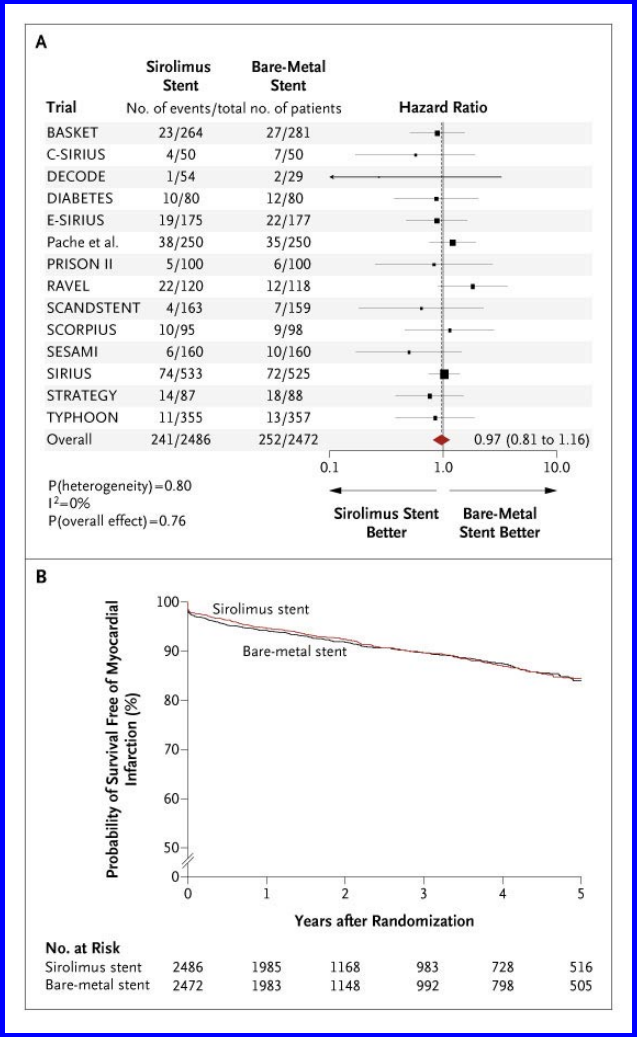


8 of these trials censored secondary stent thrombosis

Stent thrombosis defined by study protocol not by ARC criteria

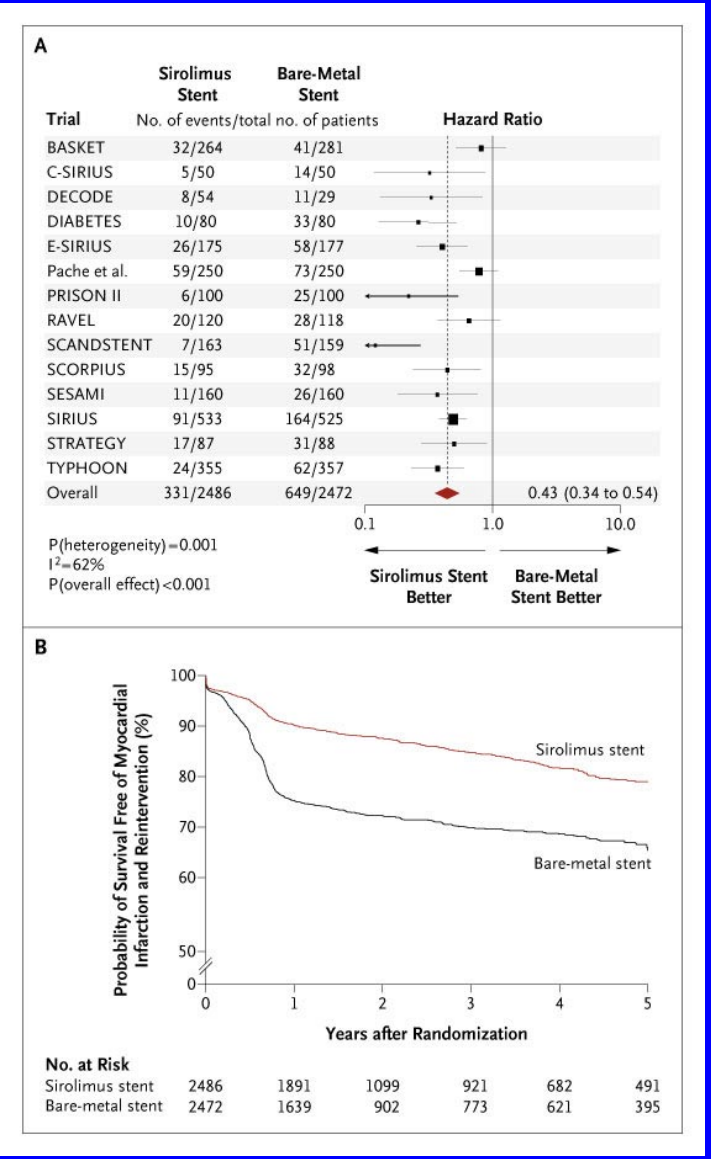
Kastrati A et al. N Engl J Med 2007;356:1030-1039

Death or MI and Survival Free of MI



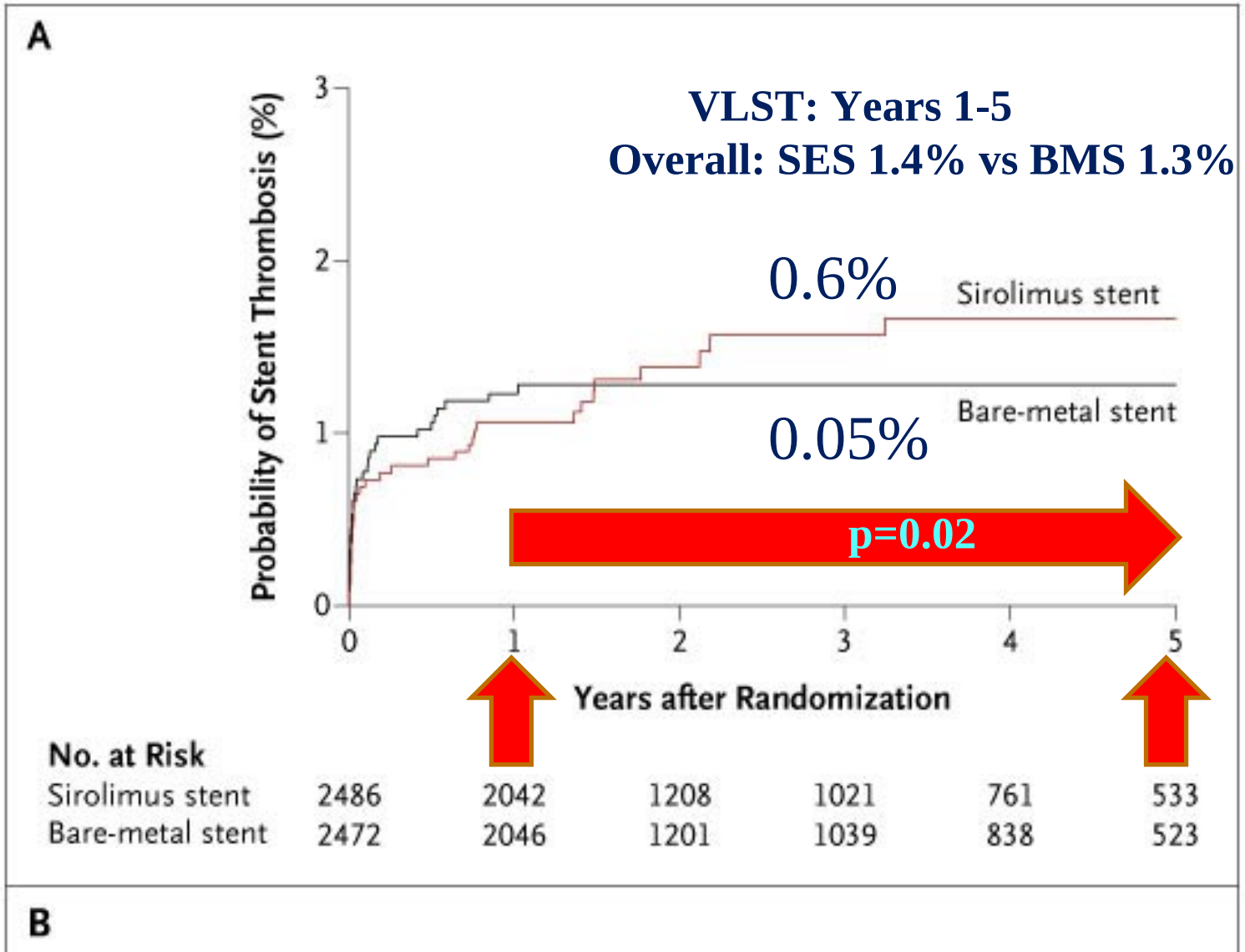
Kastrati A et al. N Engl J Med 2007;356:1030-1039

Survival Free of MI and Reintervention



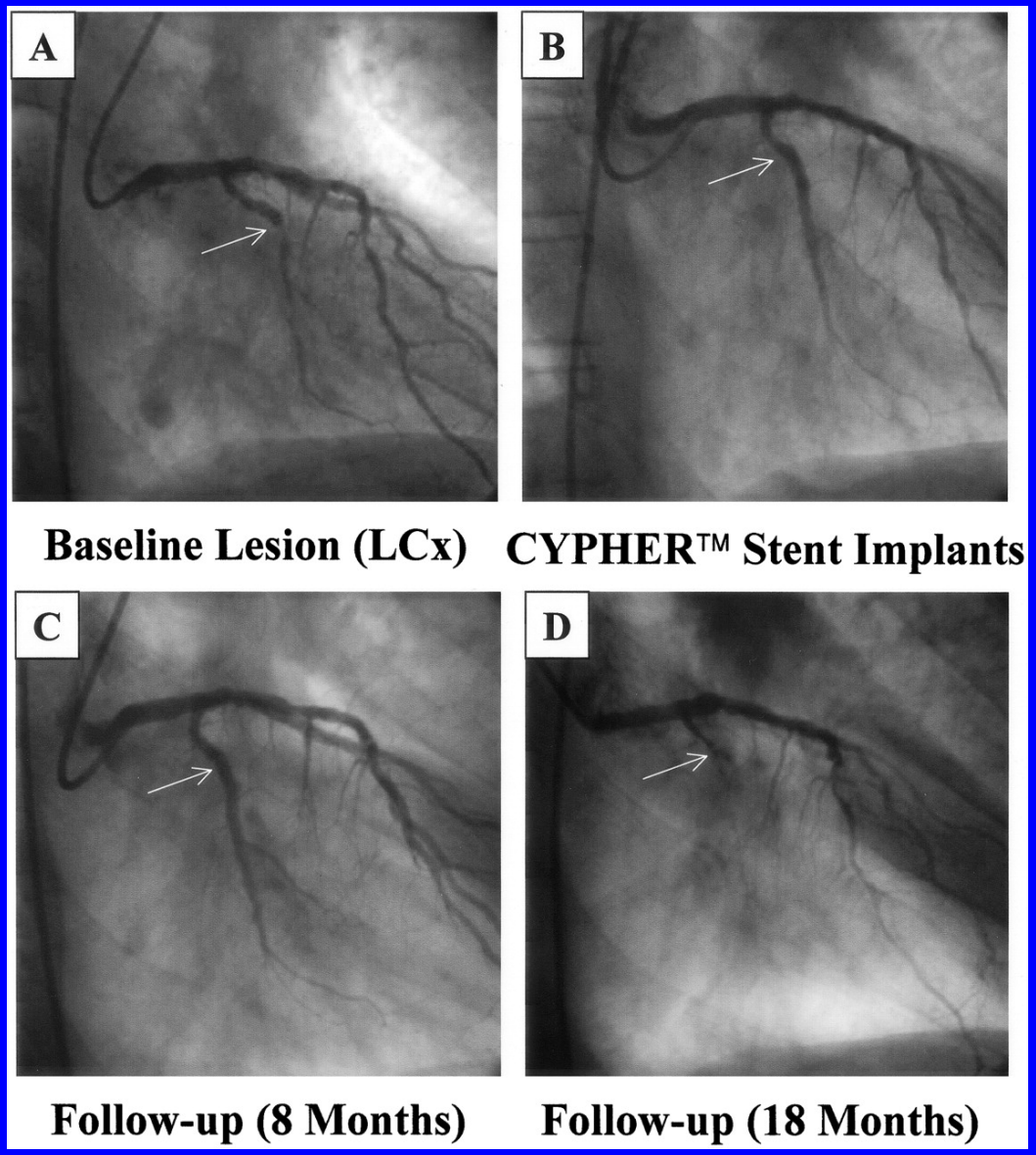
Kastrati A et al. N Engl J Med 2007;356:1030-1039

BMS vs SES:
Stent Thrombosis: Timing



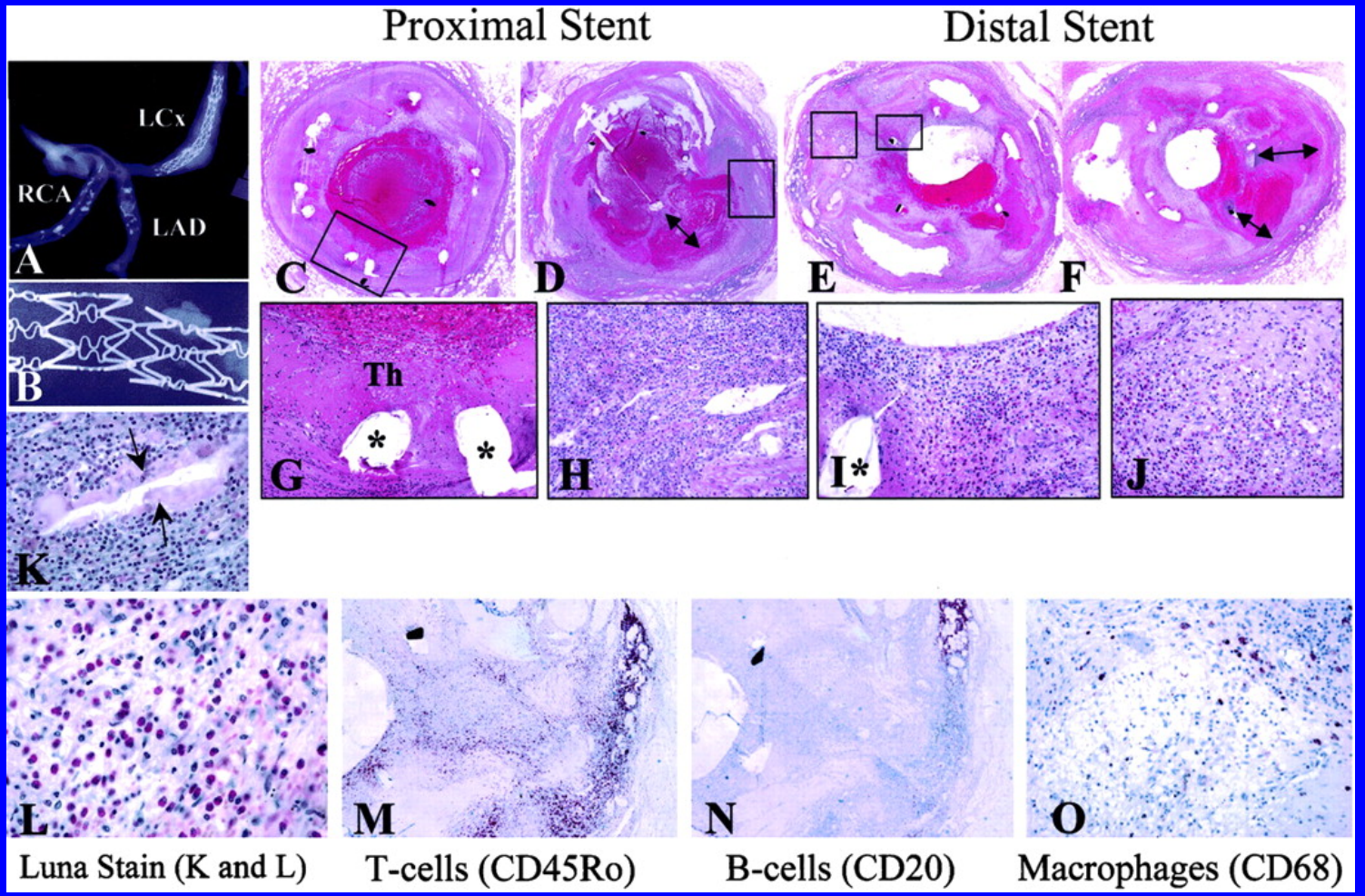
Kastrati A et al. N Engl J Med 2007;356:1030-1039

So, when it happens……



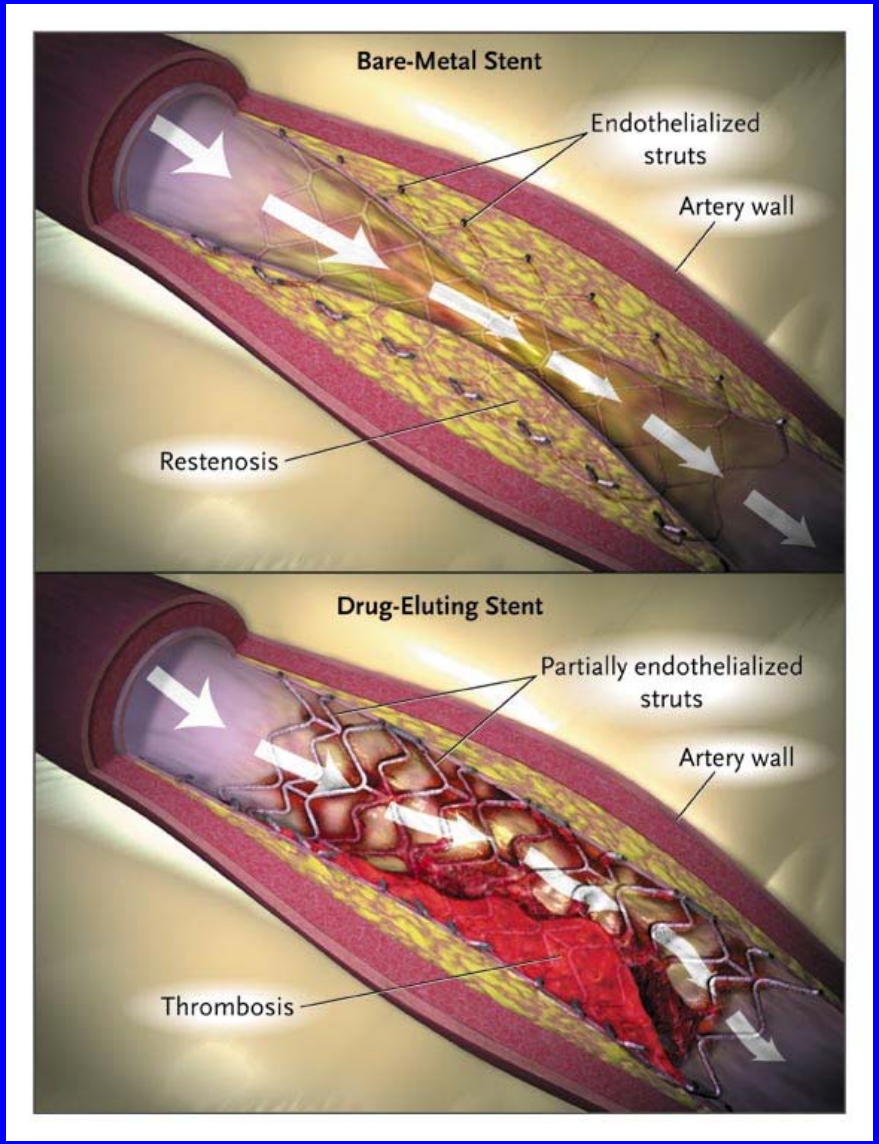
Virmani, R. et al. Circulation 2004;109:701-705

Why does it happen?



Virmani, R. et al. Circulation 2004;109:701-705

Mechanism: Inflammation, malapposition, thrombosis



Suboptimal stent deployment: just as likely with DES as with BMS

More challenging lesions, smaller vessels

Polymer induced hypersensitivity with eosinophilic infiltration (probably not to stent or drug)

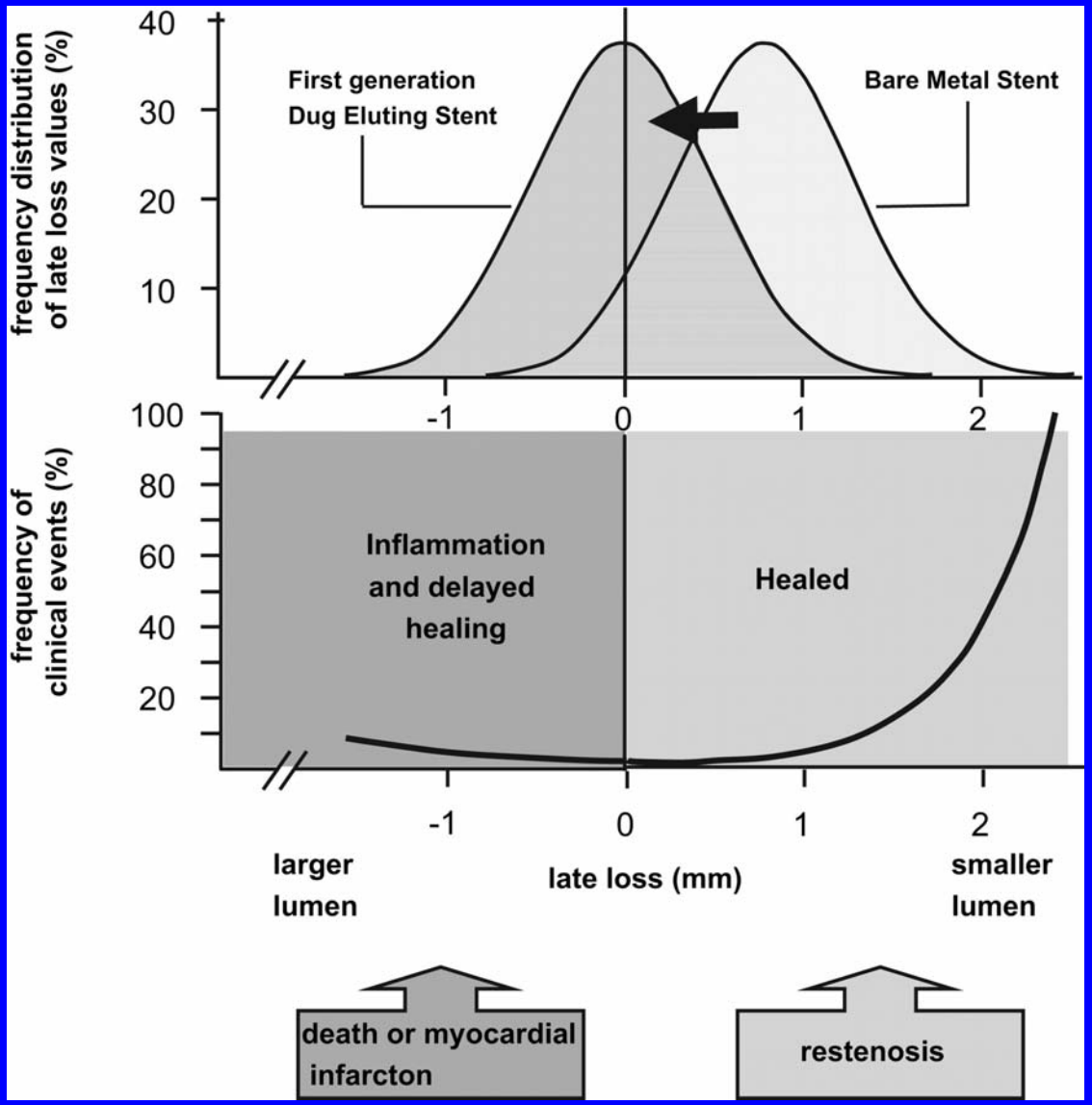
Inflammation may prevent endothelialization of the stent and may causes destruction of the media

Positive remodeling causing late acquired stent malapposition (LASMA) in 10% and coronary aneurysm in 1%

Curfman G et al. N Engl J Med 2007;356:1059-1060

Virmani, R. et al. Circulation 2004;109:701-705

J-curve relationship between Late Loss and clinical events



Camenzind, E. et al. Circulation 2007;115:1440-14

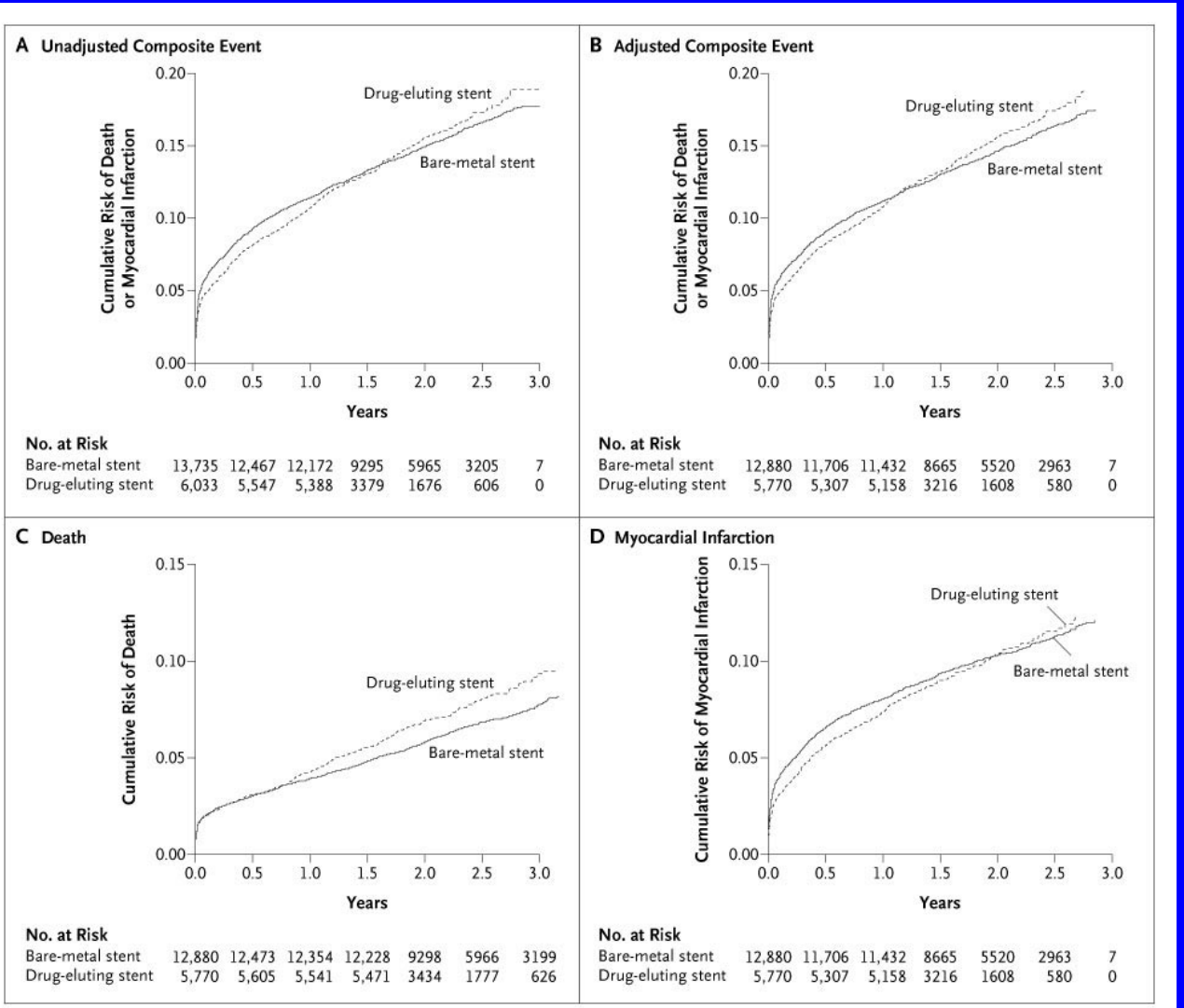
Conclusions

- A small increase in the incidence of very late stent thrombosis (after 1 year) with DES compared to BMS when protocol but not ARC definition is used
- No evidence of associated increased mortality or MI with DES versus BMS
- Reconfirmation of the marked benefit of DES upon the need to repeat revascularization
- Trade off ? A frequent, innocuous (restenosis) versus a rare malignant (stent thrombosis) outcome.

Limitations of the data and Unanswered Questions

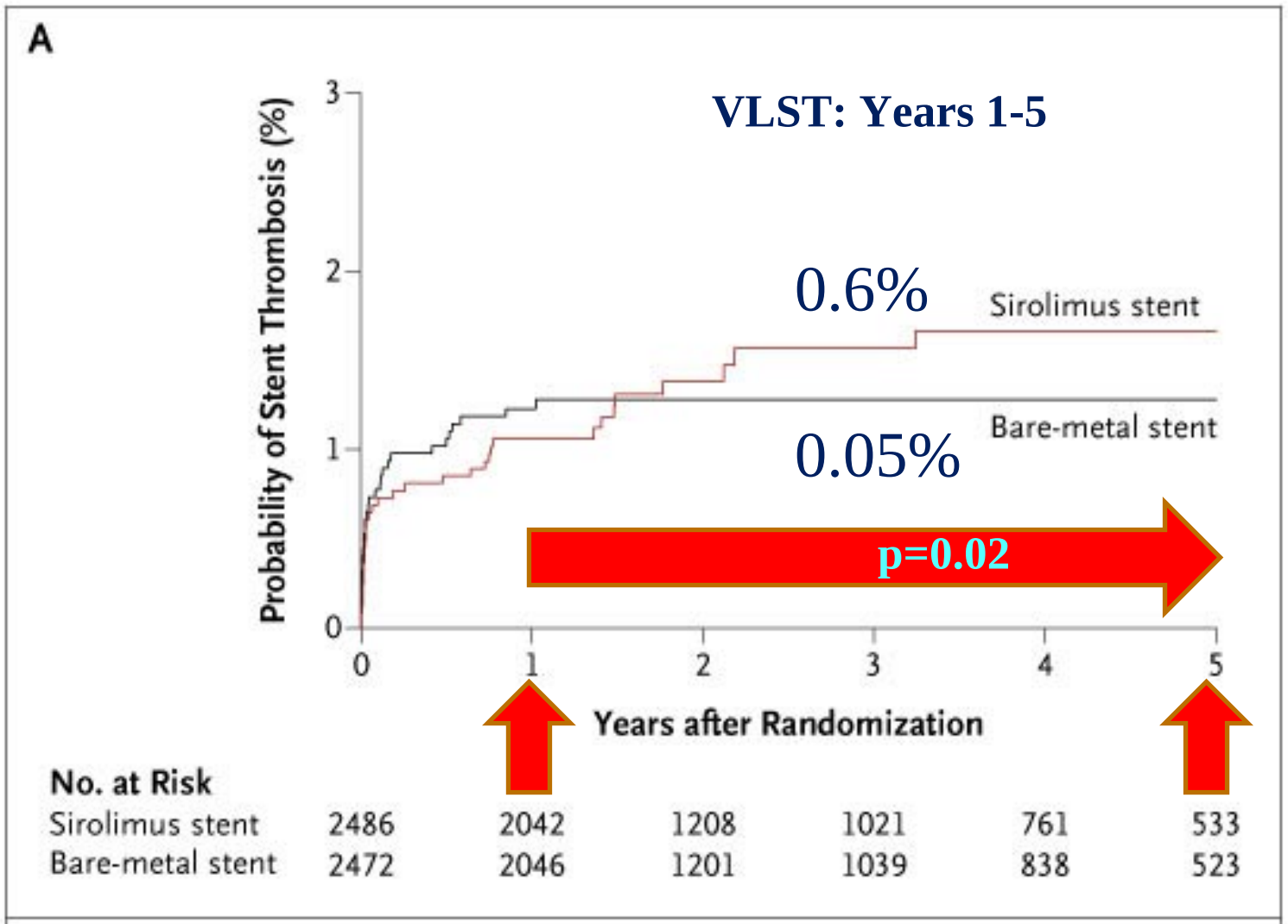
- Study not powered to detect a clinically significant mortality difference: 11,000 patients would need to be studied to be able to detect a mortality effect
- Longer term follow up needed
- Patients are highly selected and represent only 25% of patients currently treated with DES: Do these (reassuring?) data apply to all the rest in the “real world”?
- Dual antiplatelet therapy

Real World: SCAAR
Estimated Cumulative Event Rates



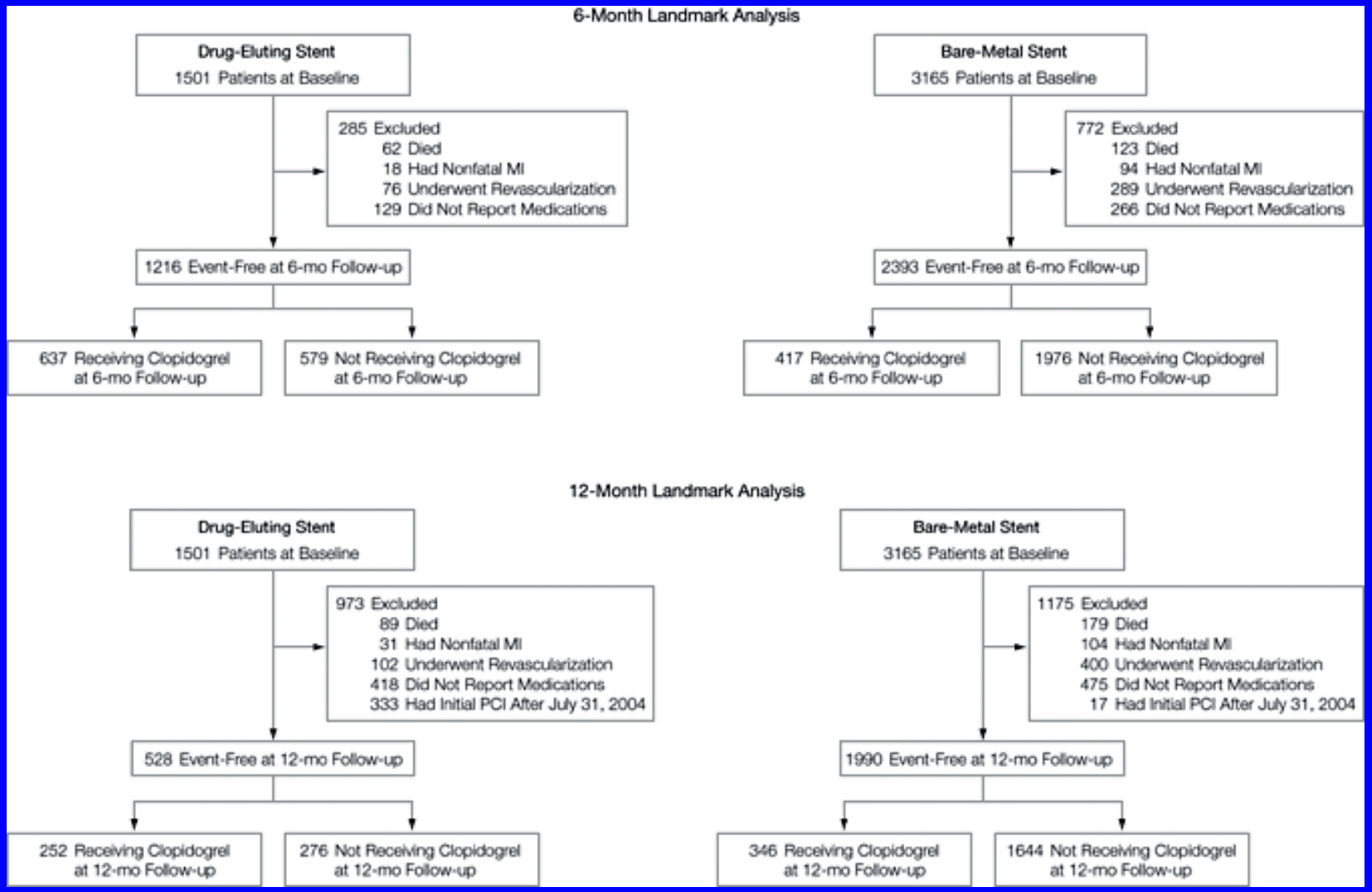
Lagerqvist B et al. N Engl J Med 2007;356:1009-1019

VLST: Is it related to cessation of Dual Anti-Platelet therapy?



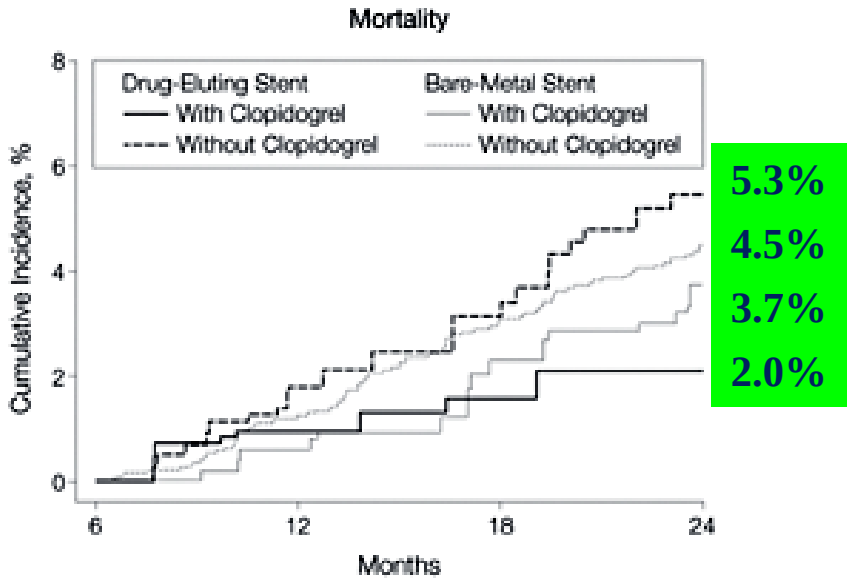
Kastrati A et al. N Engl J Med 2007;356:1030-1039

VLST:
Is the risk lessened by longer duration of Dual Anti-Platelet Therapy?

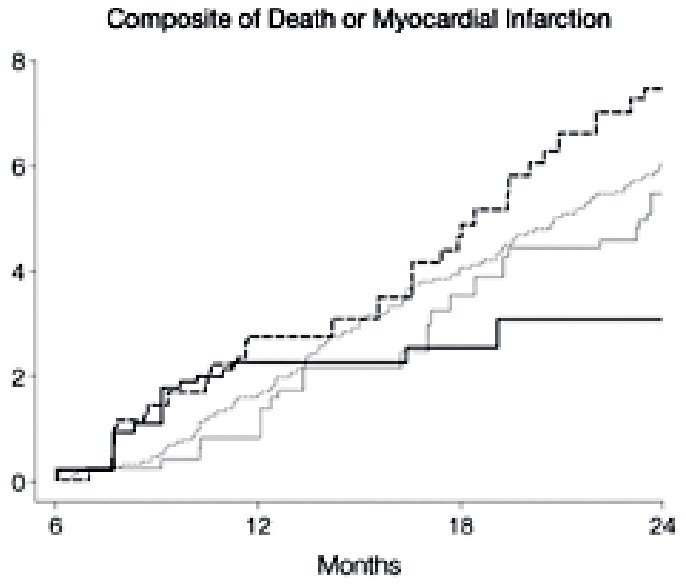


Eisenstein, E. L. et al. JAMA 2007;297:159-168.

VLST:
Is the risk lessened by longer duration of Dual Anti-Platelet Therapy?



5.3%
4.5%
3.7%
2.0%



No. at Risk								
Drug-Eluting Stent								
With Clopidogrel	637	618	303	290	637	613	300	287
Without Clopidogrel	579	532	267	245	579	526	262	238
Bare-Metal Stent								
With Clopidogrel	417	413	397	387	417	412	394	382
Without Clopidogrel	1976	1948	1896	1852	1976	1941	1879	1825

DES with vs without Clopidogrel p=0.03

BMS with vs without Clopidogrel p=0.5 NS

Eisenstein, E. L. et al. JAMA 2007;297:159-168.

What is the appropriate duration of Dual Anti-Platelet Therapy after DES?

- Not known
- Trials will be needed and have been proposed
- Until then: individualized
- Risk, cost and compliance issuesassociated with long-term dual anti-platelet therapy

Implications for ongoing trials of DES

Randomized Studies of Currently Approved Drug-Eluting Stents That May Result in Expansion of Indications for Use.*

Trial	Conditions	Treatment Groups	Expected Total Enrollment	Design	Primary End Point	Date Initiated
Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX [ClinicalTrials.gov no., NCT00114972])†	Multivessel coronary disease or disease of the left main coronary artery	Multivessel Taxus stents vs. CABG	1800	Noninferiority	12-mo rate of major adverse cardiac and cerebrovascular events (death from any cause, cerebrovascular event, myocardial infarction, or repeated revascularization)	March 2005
Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM [ClinicalTrials.gov no., NCT00086450])†	Multivessel coronary disease and diabetes mellitus	Multivessel Cypher or Taxus stents vs. CABG	2400	Superiority	Composite of death from any cause, nonfatal myocardial infarction, or stroke measured through 5 yr (minimum of 3 yr of follow-up)	April 2004
Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI)‡	Myocardial infarction with acute ST-segment elevation	Taxus stent vs. identical bare-metal Express stent	3400	Superiority	Efficacy: ischemic target-vessel revascularization at 1 yr Safety: composite of death, reinfarction, stent thrombosis, or stroke at 1 yr	March 2005

* PCI denotes percutaneous coronary intervention, and CABG coronary-artery bypass grafting.
† Information is from ClinicalTrials.gov.
‡ Registration of this trial at ClinicalTrials.gov is pending.

Farb A and Boam A. N Engl J Med 2007;356:984-987

Which brings us to our next controversy: Should we be stenting all these patients in the first place?

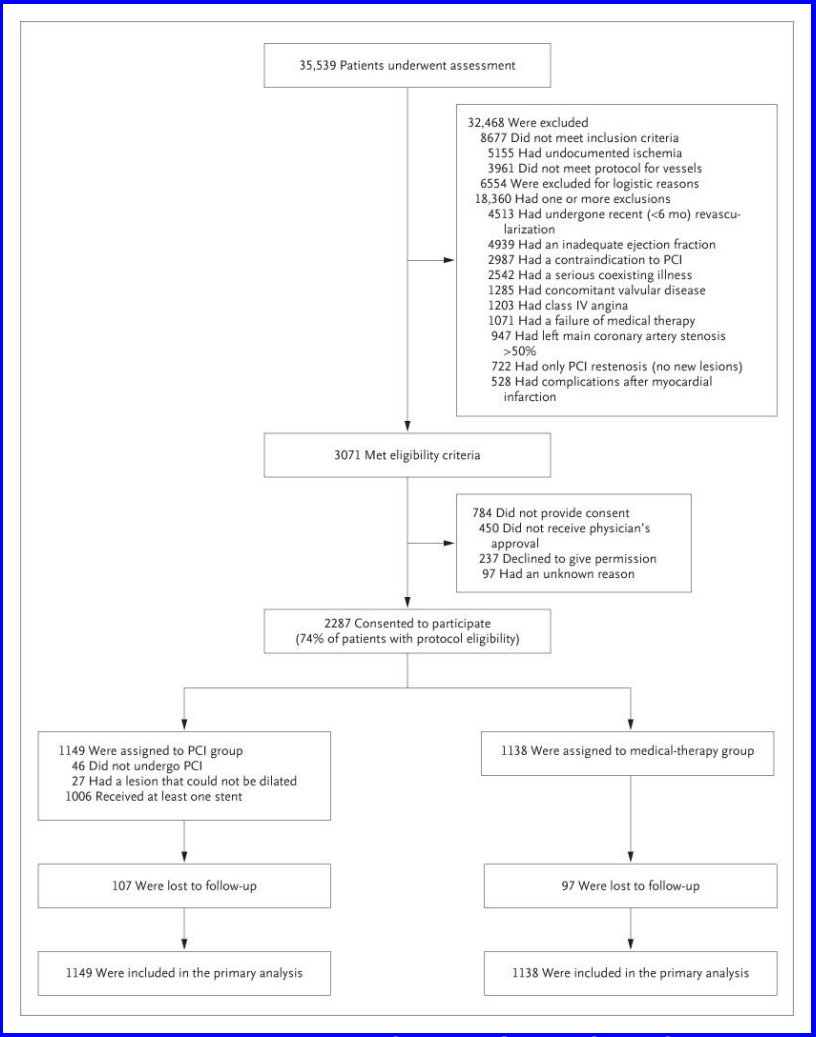
- Courage Trial Research Group
- Stable coronary artery disease
- Should the initial management strategy be PCI or intensive medical and lifestyle intervention?

Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation COURAGE Trial: Enrollment and Outcomes

Stable coronary artery disease with:

70% stenosis in a proximal epicardial coronary artery with objective evidence of myocardial ischemia

Or, 80% stenosis with typical anginal symptoms without the need for documentation of ischemia



Boden W et al. N Engl J Med 2007;10.1056/NEJMoa07082

Primary and Secondary Outcomes
Median follow up of 4.6 years

Table 3. Primary and Secondary Outcomes.*

Outcome	Number of Events		Hazard Ratio (95% CI)†	P Value†	Cumulative Rate at 4.6 Years	
	PCI Group	Medical-Therapy Group			PCI Group	Medical-Therapy Group
					%	
Death and nonfatal myocardial infarction‡	211	202	1.05 (0.87–1.27)	0.62	19.0	18.5
Death§	68	74				
Periprocedural myocardial infarction	35	9				
Spontaneous myocardial infarction	108	119				
Death, myocardial infarction, and stroke	222	213	1.05 (0.87–1.27)	0.62	20.0	19.5
Hospitalization for ACS	135	125	1.07 (0.84–1.37)	0.56	12.4	11.8
Death§	85	95	0.87 (0.65–1.16)	0.38	7.6	8.3
Cardiac	23	25				
Other	45	51				
Unknown	17	19				
Total nonfatal myocardial infarction	143	128	1.13 (0.89–1.43)	0.33	13.2	12.3
Periprocedural myocardial infarction	35	9				
Spontaneous myocardial infarction	108	119				
Death, myocardial infarction, and ACS	294	288	1.05 (0.90–1.24)	0.52	27.6	27.0
Stroke	22	14	1.56 (0.80–3.04)	0.19	2.1	1.8
Revascularization (PCI or CABG)¶	228	348	0.60 (0.51–0.71)	<0.001	21.1	32.6

* ACS denotes acute coronary syndrome, PCI percutaneous coronary intervention, and CABG coronary-artery bypass grafting.
† The hazard ratio is for the PCI group as compared with the medical-therapy group, and P values were calculated by the log-rank test and are unadjusted for multiple variables.
‡ The definition of myocardial infarction was the finding of new Q waves at any time; a spontaneous creatine kinase MB fraction of at least 1.5 times the upper limit of normal or a troponin T or I level of at least 2.0 times the upper limit of normal; during a PCI procedure, a creatine kinase MB fraction of at least 3 times the upper limit of normal or a troponin T or I level of at least 5.0 times the upper limit of normal, associated with new ischemic symptoms; and after CABG, a creatine kinase MB fraction or a troponin T or I level of at least 10.0 times the upper limit of normal. If periprocedural myocardial infarction is excluded from the primary outcome, the hazard ratio is 0.90 (95% CI, 0.73 to 1.10; P=0.29).
§ Some patients had a nonfatal myocardial infarction before their subsequent death so that the number of deaths overall is greater than the number of deaths in the primary outcome analysis, which includes the time until the first event.
¶ Values exclude the initial PCI procedure in patients who were originally assigned to the PCI group.

Boden W et al. N Engl J Med 2007;10.1056/NEJMoa070829

Clinical Status, Risk and Lifestyle Factors, and Use of Medication

Table 2. Clinical Status, Risk and Lifestyle Factors, and Use of Medication.*

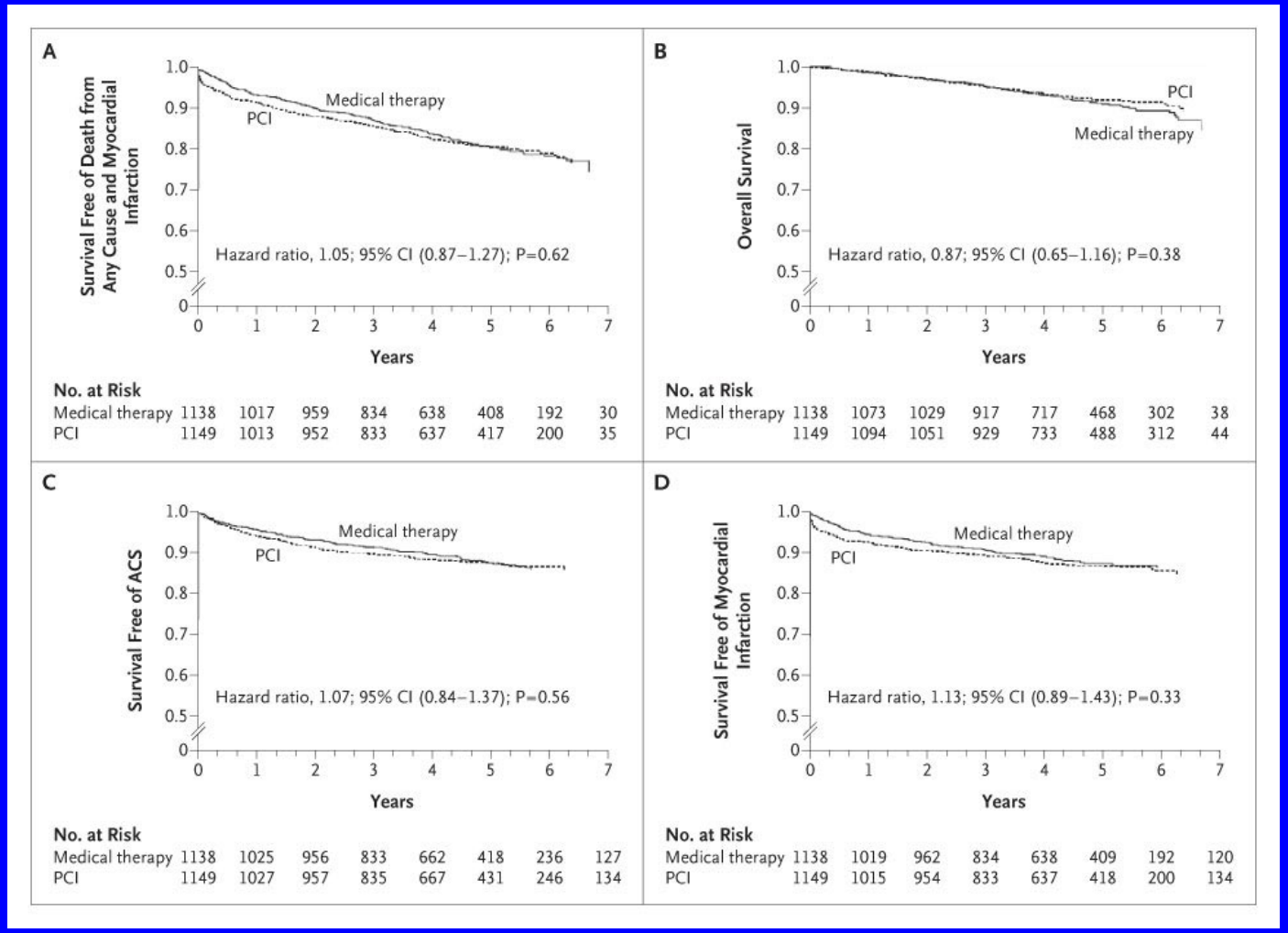
Variable	PCI Group (N=1149)				Medical-Therapy Group (N=1138)			
	Baseline	1 Yr	3 Yr	5 Yr	Baseline	1 Yr	3 Yr	5 Yr
	median ±SE							
Clinical status								
No. evaluated	1148	1031	820	423	1137	1010	824	406
Blood pressure — mm Hg								
Systolic	131±0.77	126±0.64	125±0.68	124±0.81	130±0.66	124±0.73	123±0.78	122±0.92
Diastolic	74±0.33	72±0.35	70±0.52	70±0.81	74±0.33	70±0.43	70±0.52	70±0.65
Cholesterol — mg/dl								
Total	172±1.37	156±1.17	148±1.13	143±1.74	177±1.41	150±1.10	145±1.30	140±1.64
HDL	39±0.39	42±0.39	43±0.47	41±0.67	39±0.37	41±0.42	42±0.49	41±0.75
LDL	100±1.17	84±0.97	76±0.85	71±1.33	102±1.22	81±0.86	74±0.92	72±1.21
Triglycerides — mg/dl	143±2.96	129±2.74	124±2.79	123±4.13	149±3.03	133±2.90	126±2.84	131±4.70
Body-mass index	28.7±0.18	28.5±0.19	29.0±0.21	29.0±0.34	28.9±0.17	29.0±0.19	29.3±0.21	29.5±0.31
Angina-free — no. (%)†	135 (12)	680 (66)	602 (72)	316 (74)	148 (13)	595 (58)	558 (67)	296 (72)
Risk or lifestyle factor								
Current smoker — no. (%)	260 (23)	206 (20)	156 (19)	74 (17)	259 (23)	206 (20)	160 (19)	80 (20)
AHA Step 2 diet — no. (%)	626 (55)	803 (78)	631 (77)	326 (77)	613 (54)	800 (79)	660 (80)	312 (77)
Moderate activity — no. (%)‡	290 (25)	473 (46)	351 (42)	179 (42)	279 (25)	433 (43)	330 (40)	146 (36)
Glycated hemoglobin in patients with diabetes								
No. evaluated	319	239	197	97	336	286	233	123
Level — %	6.9±0.1	7.1±0.1	7.1±0.1	7.1±0.1	7.1±0.1	7.0±0.1	7.1±0.1	7.1±0.1
Medication								
No. evaluated	1147	1044	837	428	1138	1028	838	417
ACE inhibitor — no. (%)	669 (58)	668 (64)	536 (64)	284 (66)	680 (60)	633 (62)	522 (62)	260 (62)
ARB — no. (%)	48 (4)	93 (9)	104 (12)	49 (11)	54 (5)	99 (10)	108 (13)	67 (16)
Statin — no. (%)	992 (86)	972 (93)	780 (93)	398 (93)	1014 (89)	972 (95)	769 (92)	386 (93)
Other antilipid — no. (%)	89 (8)	236 (23)	324 (39)	211 (49)	94 (8)	253 (25)	321 (38)	224 (54)
Aspirin — no. (%)	1097 (96)	995 (95)	792 (95)	408 (95)	1077 (95)	977 (95)	796 (95)	391 (94)
Beta-blocker — no. (%)	975 (85)	887 (85)	705 (84)	363 (85)	1008 (89)	916 (89)	724 (86)	357 (86)
Calcium-channel blocker — no. (%)§	459 (40)	415 (40)	360 (43)	180 (42)	488 (43)	501 (49)	418 (50)	217 (52)
Nitrates — no. (%)¶	714 (62)	553 (53)	396 (47)	173 (40)	825 (72)	690 (67)	511 (61)	237 (57)

* Plus–minus values are medians ±SE, with the SE calculated with the use of the interquartile range. To convert cholesterol values to milli-

Significant at 1 and 3 years but not at 5 years

Boden W et al. N Engl J Med 2007;10.1056

Kaplan-Meier Survival Curves

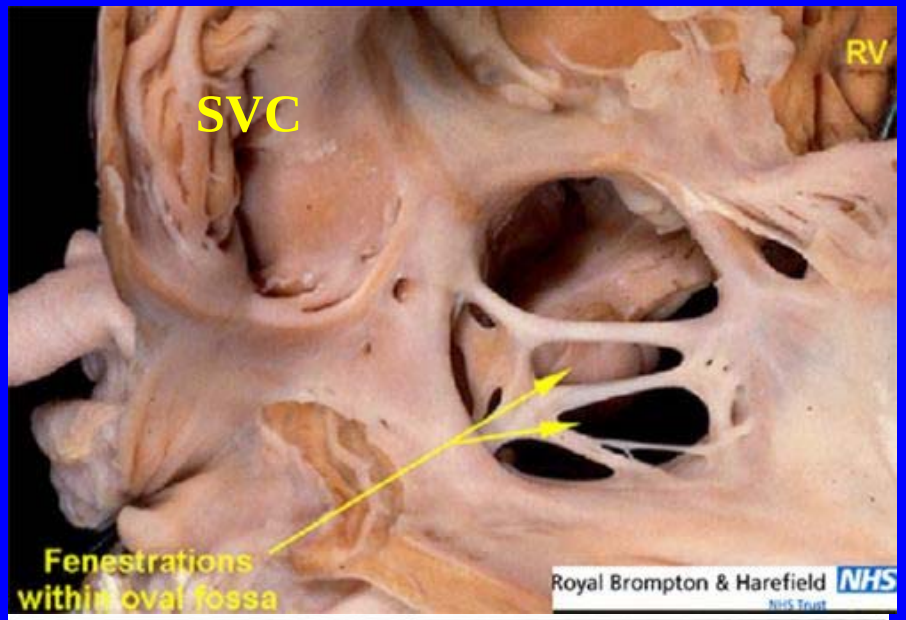


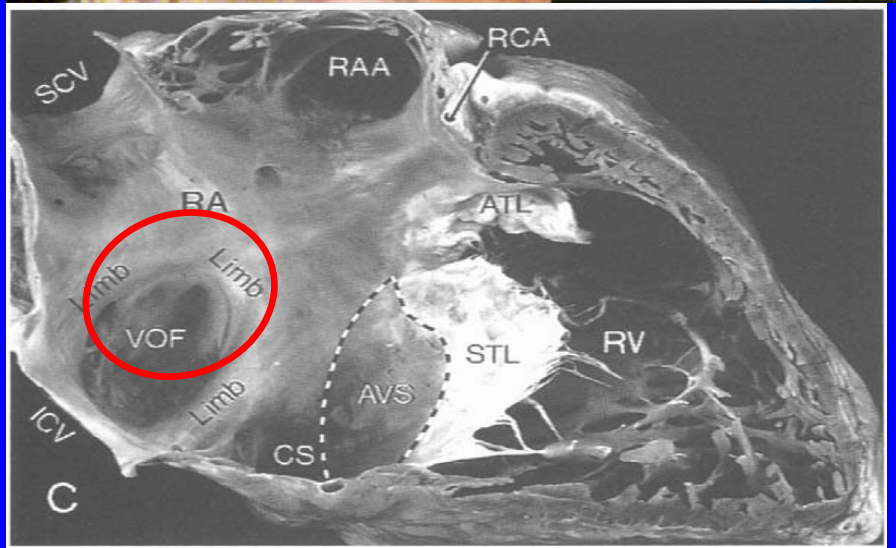
Boden W et al. N Engl J Med 2007;10.1056/NEJMoa070829

Defects of the Cardiac Interatrial Septum

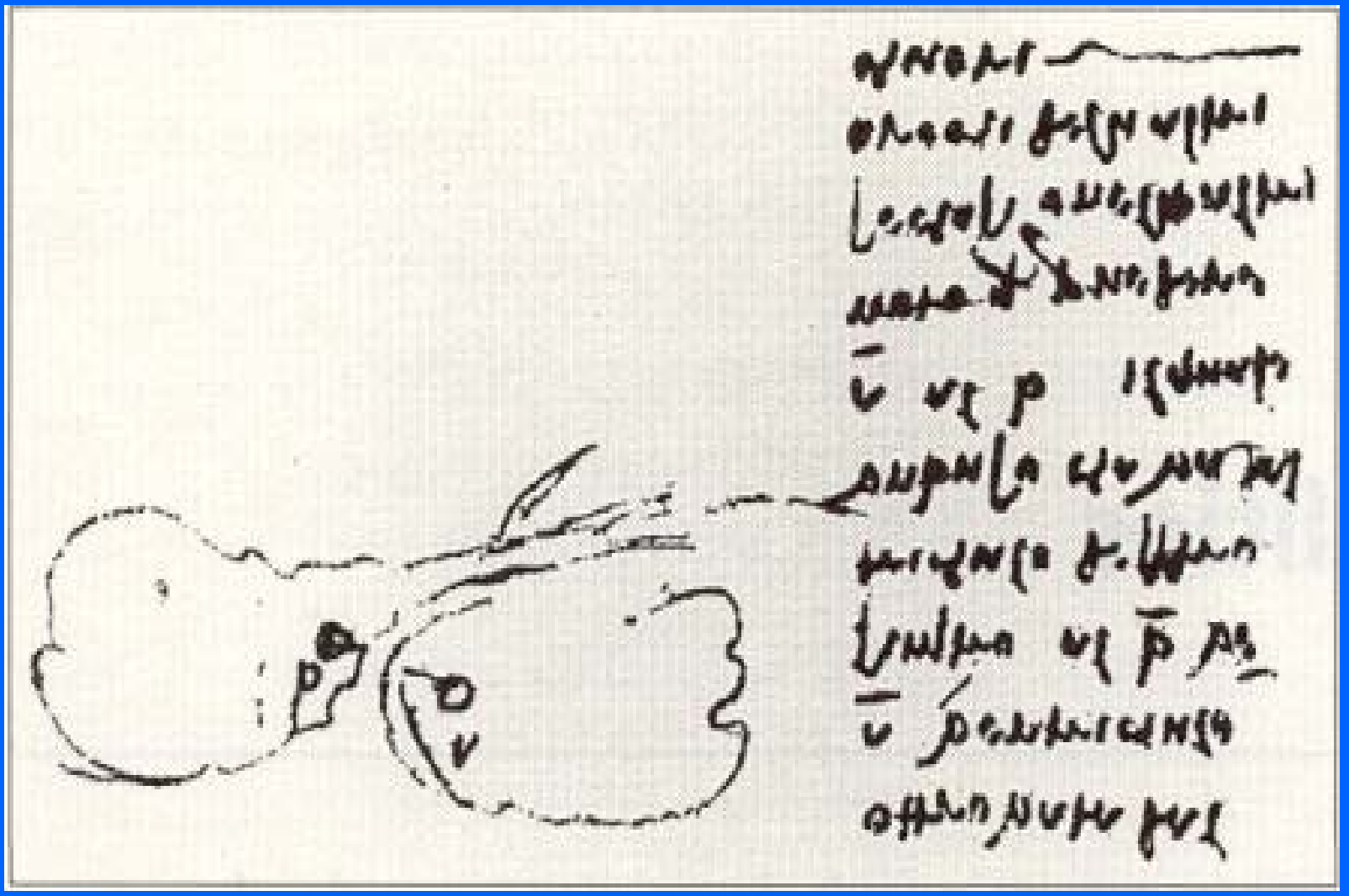
- Atrial septal defect
- Patent foramen ovale
- Atrial septal aneurysm

Secundum ASD





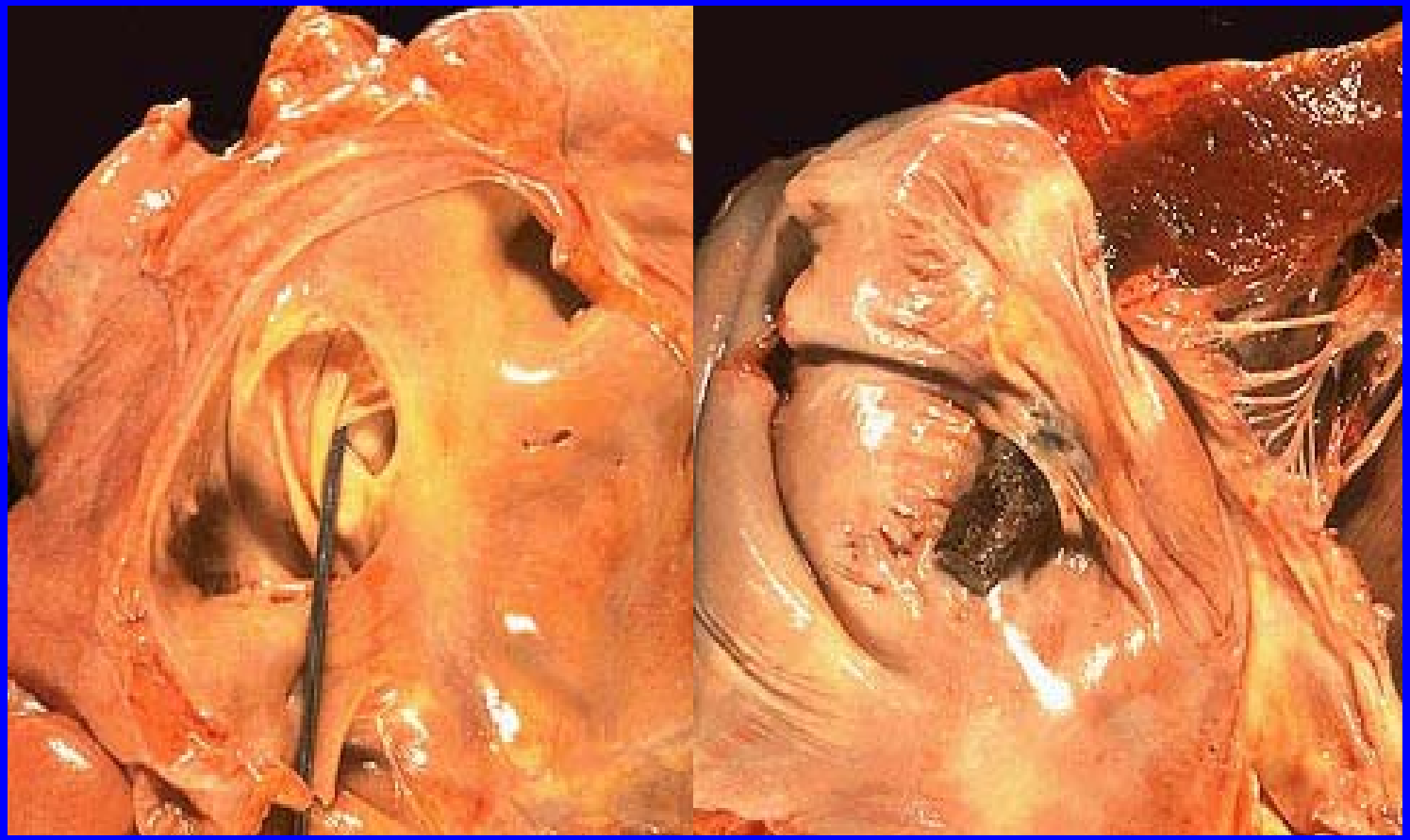
Alex Davidson MD



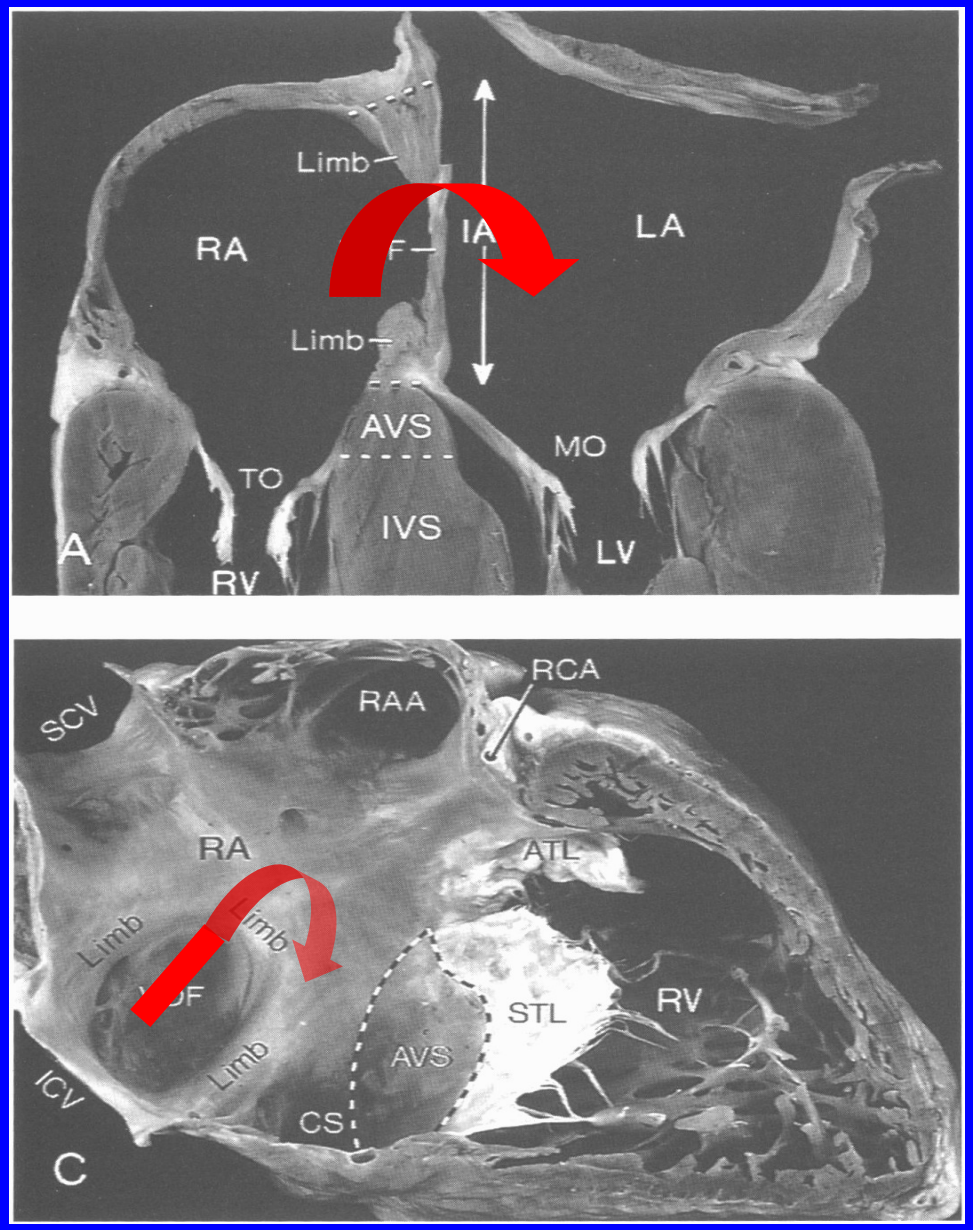
Leonardo da Vinci ; Patent foramen ovale

Potential for Paradoxical Embolism

Res ipsa loquitur



Patent foramen ovale



- The apposing portions of the valve of the foramen ovale and the septum secundum gradually fuse
- This is complete by age 2 in 75% of people
- In 25% of people, fusion fails to occur and a residual tunnel persists (patent foramen ovale)

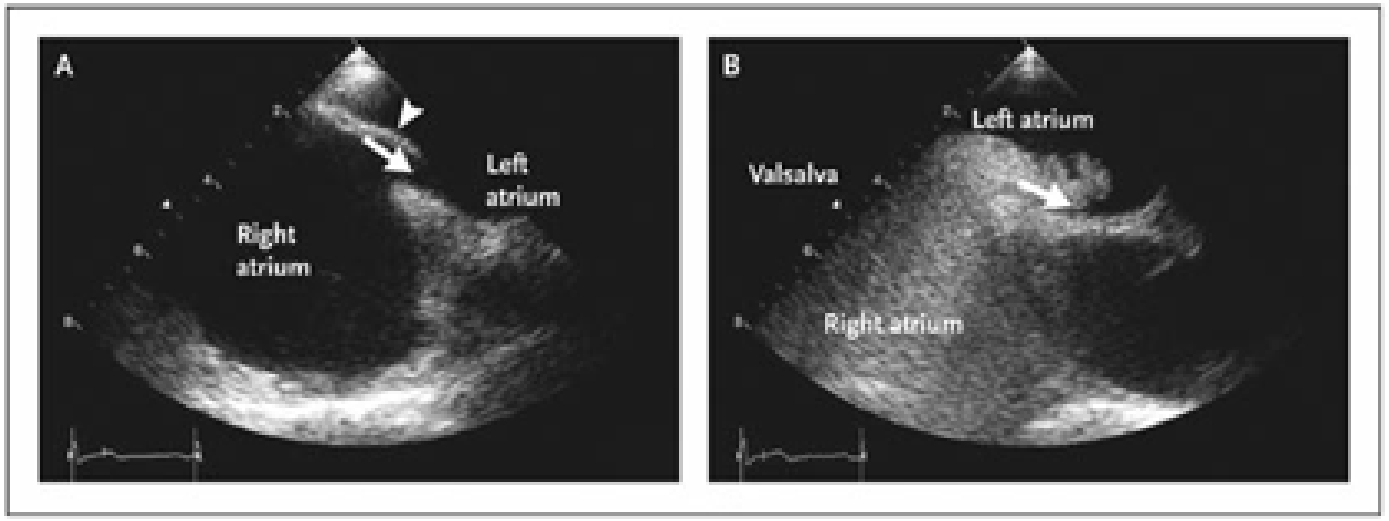
Edwards: Atrial septum

Autopsy Study of PFO

- Overall incidence 27.3% (263/965)
- No gender differences
- Progressive decline in incidence with increasing age
- Progressive increase in size of PFO with increasing age
- Mean PFO diameter 4.9 mm
  - range 1-19 mm
  - 1-10 mm in 98%

Hagen et al Mayo Clin Proc 1984;59:17-20

Bubble study with Valsalva: Right to Left Shunting



Kizer et al N Engl J Med 2005;353:2361-72

Amplatzer PFO Occluder

- Nitinol (nickel titanium alloy) mesh double-disk containing polyester fabric
- The disks are connected by a thin neck

AGA Medical, Golden Valley MN

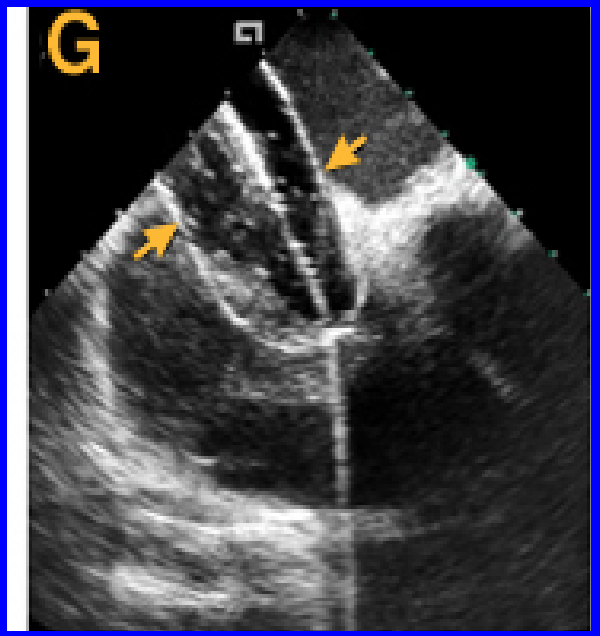
CardioSEAL

- Double umbrella with 4 arms
- Dacron patches fixed to 2 nitinol cross bars
- The wires spreading the tissue have joints made of spring coils
- STARFlex: self centering, 4-6 arms
  (not available on HDE but is being used in clinical research)

NMT Medical, Boston MA

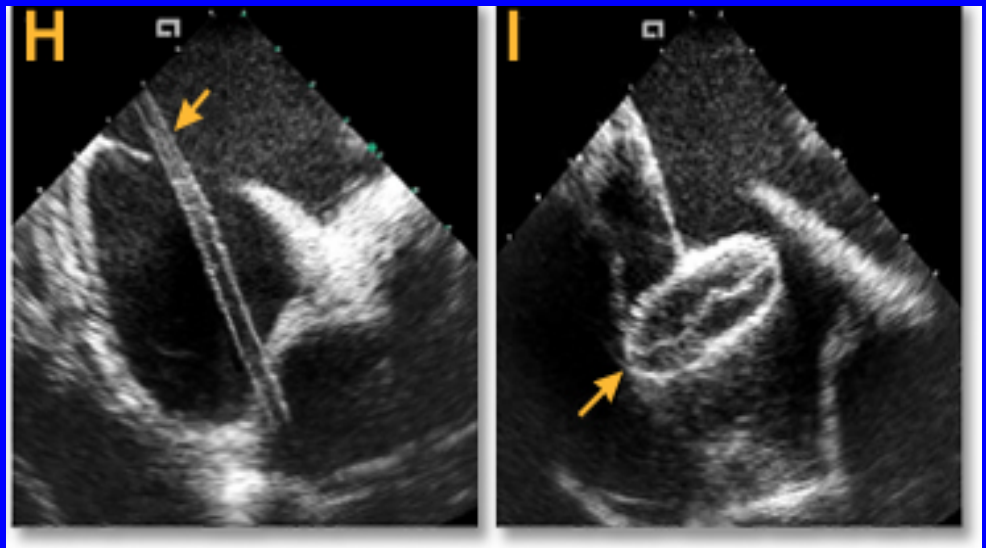
Percutaneous Closure

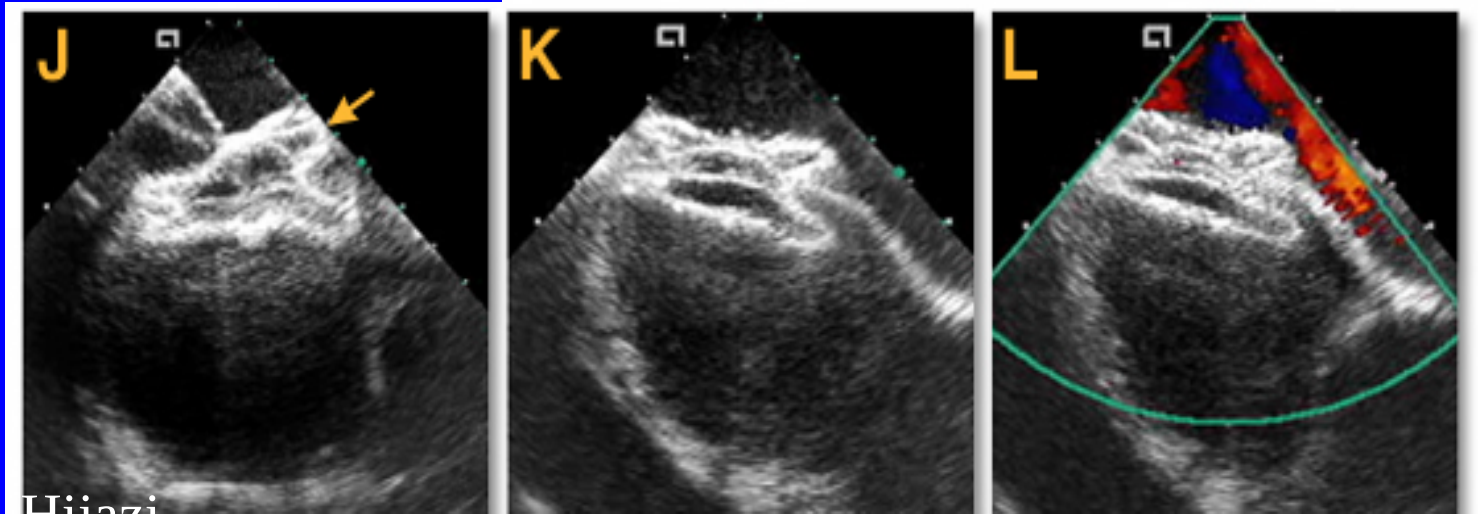
- Venous sheath 12-14 Femoral
- TEE guidance with general anesthesia
- Intracardiac echo (ICE)
- Balloon sizing



Percutaneous Closure

Device is deformable and is pulled into a loader and passed up to the left atrium through a delivery sheath





Endothelialization

Sharafuddin et al Circulation 1997;95:2162-8

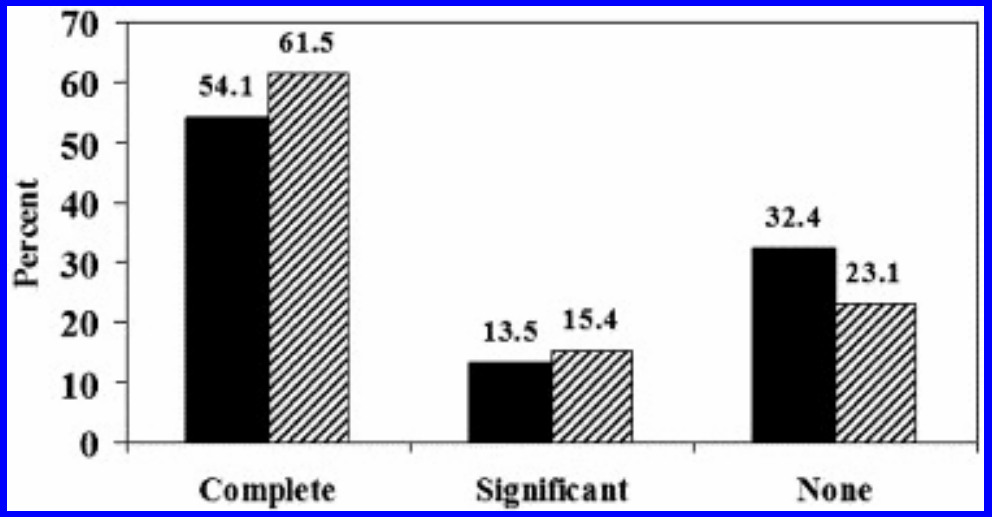
Suspected Role for Patent Foramen Ovale

- Paradoxical embolism (Stroke)
- Migraine
- Right-to-left shunting causing hypoxia
- Platypnea-Orthodeoxyia
- Decompression sickness

Migraine: Where did this come from?

- PFO is associated with higher prevalence of migraine than in those without PFO
- PFO and other atrial shunts may have genetic/familial links to migraine
- PFO closure after cryptogenic stroke has been associated with an unexpected reduction in migraine headaches in those with aura

Effect of PFO Closure on Relief of Migraine



56% **14%** **30%**

57 patients with migraine
39/57 had aura (hatched bars)

Reisman et al J Am Coll Cardiol 2005;45:493-5

MIST Trial

Migraine Intervention with STARFlex Technology

MIST Trial
Migraine Intervention with STARFlex Technology

- Efficacy of PFO closure to prevent refractory migraine headaches
- First prospective, multicenter, randomized, blinded and sham-controlled trial
- 13 centers in UK from January 2005-July 2005

MIST Trial Design

- TransThoracic Echo with agitated saline
- Those with large PFO were randomized
- 1:1 randomization to closure vs. sham

MIST I

End point	PFO closure	Sham	p
Complete Headache cessation (n)	3	3	NS
50% reduction in headache days (%)	42	23	0.038
Reduced headache burden (%)	37	17	0.033

Dowson A. i2 Summit at the American College of Cardiology 2006 Scientific Sessions; March 13, 2006; Atlanta, GA.

MIST Conclusions

- PFO closure did not completely eliminate migraine, but was associated with migraine improvement.

- Limitations:
  - Length of follow up (MIST-II planned),
  - How complete was closure?
  - No prophylactic medication washout

- Future Trials
  - MIST II

Future Trials

- Premium Migraine Clinical Trial : AGA Medical

Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the AMPLATZER® PFO Occluder Compared to Medical Management

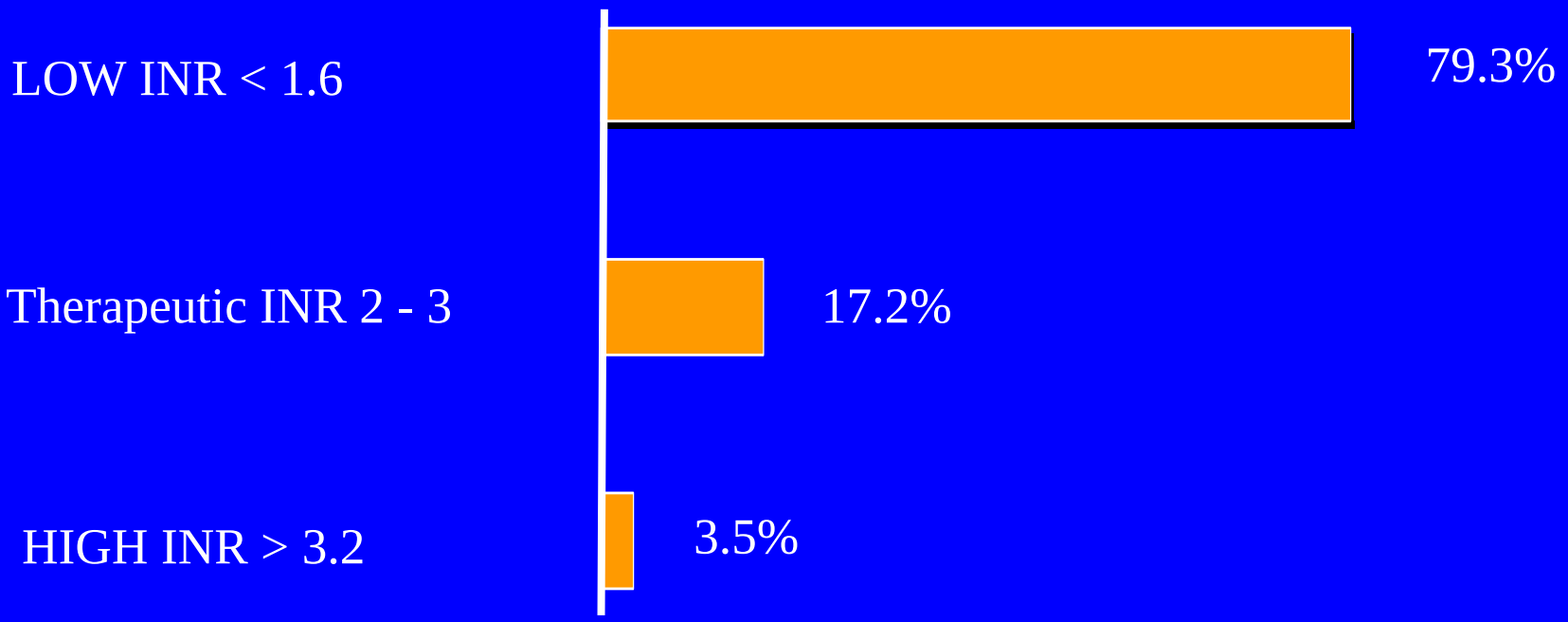
- MIST II (STARFLEX): NMT
- Escape: Effect of Septal Closure of Atrial PFO on Events of Migraine with Premere (TM)) migraine trial (St. Jude Medical)

Stroke Prevention Technology for Patients with Atrial Fibrillation

- Atrial fibrillation is a major source of cardiogenic embolism-related stroke
- 500,000 strokes per year
- AHA estimates that 15 – 20% of strokes/year are related to AF

AF Strokes: Occur primarily with sub-therapeutic INR

Adequacy of anticoagulation in patients with AF coming to a hospital clinic



Bungard. Pharmacotherapy.2001;20:1060.

Reasons for Warfarin Underutilization

- Adverse side effect profile
  - Drug & dietary interactions
- Difficulties in administration
  - Frequent blood tests
  - Narrow therapeutic range
- Patient quality of life
- Physician reluctance to prescribe to elderly patients
  - Bleeding complications
  - Risk of falling
  - Compliance issues

Left atrial appendage is a major source of thrombi that cause stroke in AF patients

- 91% of all thrombus in patients with AF is found in the left atrial appendage (LAA)
- The four largest TEE studies comprising 1,181 patients showed that 98% of thrombi were found in the LAA

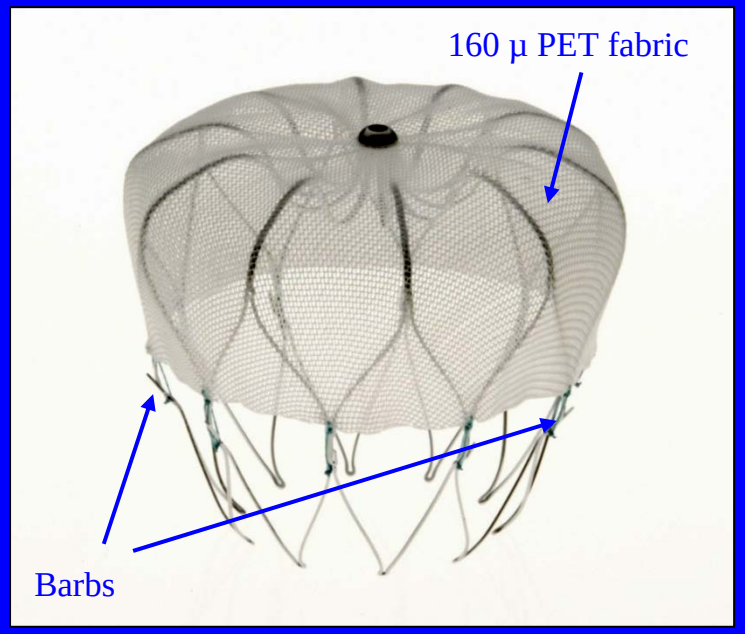
Location of thrombi in non-rheumatic atrial-fibrillation

Setting	Total # of thrombi found in LAA and atrium	Found LAA		Found in left atrium		Reference
		Number	%	Number	%	
TEE	67	66	**99%**	1	**1.5%**	*Stoddard, JACC '95*
TEE	35	34	**97**	1	**2.9**	*Manning, Circulation '94*
Autopsy	47	35	**74**	12	**25.5**	*Aberg, Acta. Med. Scan. '69*
TEE	4	2	**50**	2	**50.0**	*Tsai, JFMA '90*
TEE	13	12	**92**	1	**7.7**	*Klein, Int J. Card. Imag. '93*
TEE & operation	11	8	**73**	3	**27.3**	*Manning, Circulation '94*
SPAF III[1] & TEE	20	19	**95**	1	**5.0**	*Klein, Circulation '94*
TEE	19	19	**100**	0	**0.0**	*Leung, JACC '94*
TEE	6	6	**100**	0	**0.0**	*Hart, Stroke '94*
Total	**222**	**201**	**91%**	**21**	**9.5%**	

[1] SPAF III stands for "Stroke Prevention in Atrial Fibrillation III"

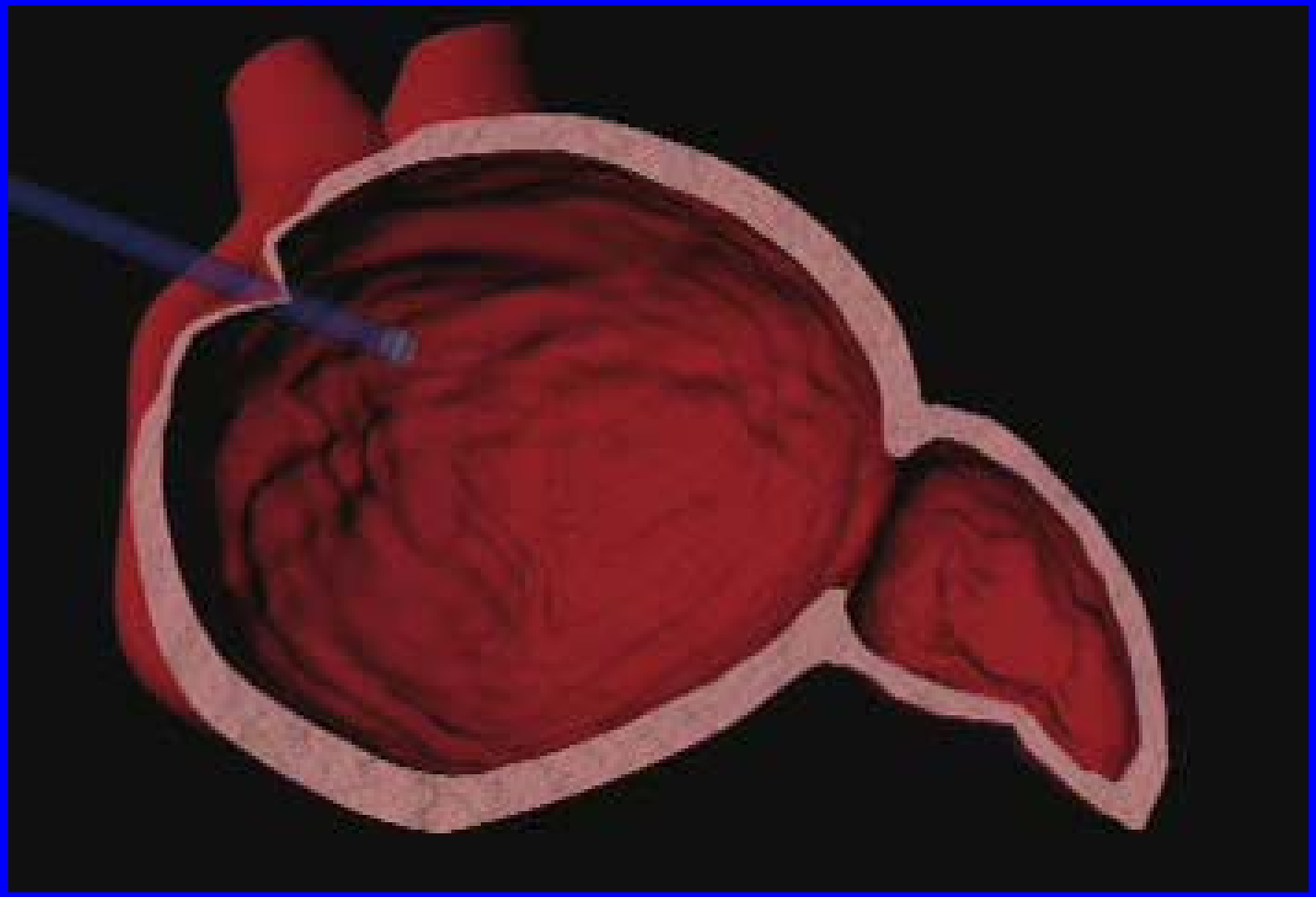
Source: *The Annals of Thoracic Surgery, 1996, 61:755–9*

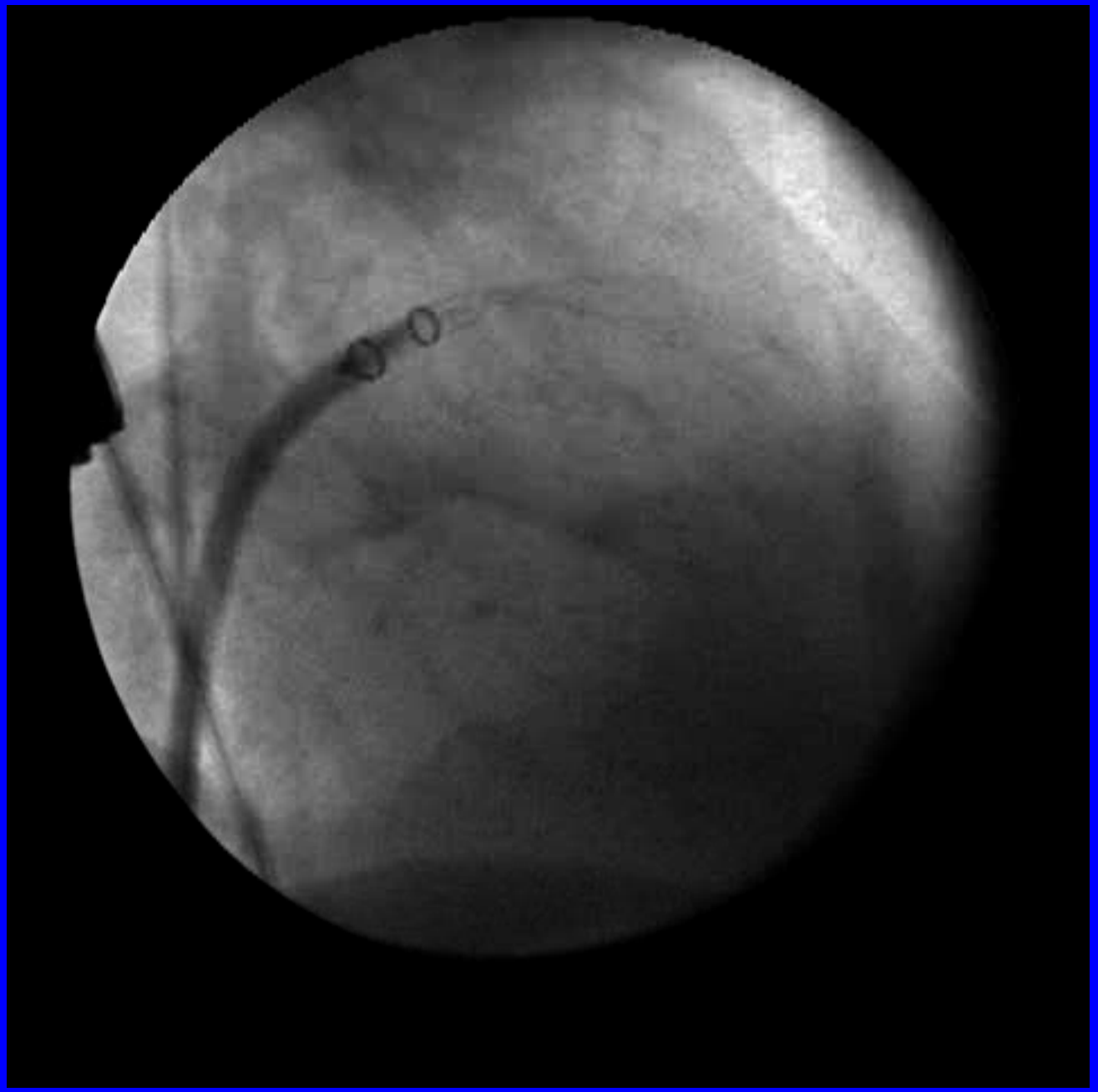
WATCHMAN® Device

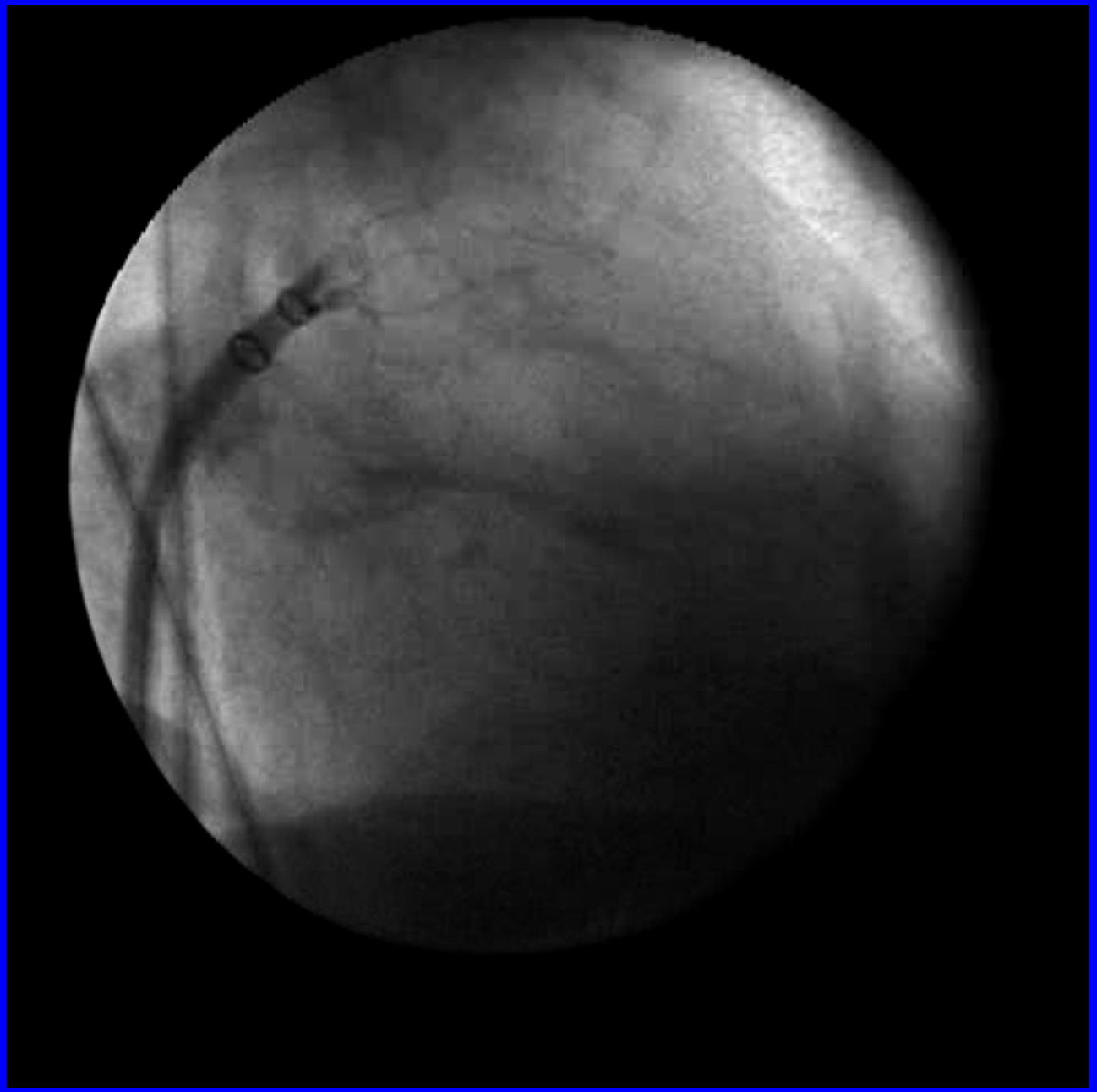


- Device available in various sizes:
  - 21, 24, 27, 30 and 33 mm (diameter)
  - Device diameter is measured across face of device
  - Device Length = Device Diameter

- **Frame:** Nitinol (shape memory)
  - Contour shape accommodates most LAA anatomy
  - Barbs engage the LAA tissue
- **Fabric Cap:** Polyethyl terephthalate (PET) Fabric
  - Prevents harmful emboli from exiting during the healing process







45 Day Follow Up

WATCHMAN® LAA System – Internal view of Complete Healing of LA

Canine – 45 days

Human @ Autopsy – 9 mos

Cribier-Edwards percutaneous valve

Webb, J. G. et al. Circulation 2006;113:842-850

Aging Population
Increasing Burden of Valve Disease

- Many patients will be poor candidates for surgical valve replacements
- Percutaneous treatments may have promise